Semester III

18BCP302 **CLINICAL BIOCHEMISTRY** **4H-4C**

Instruction hours/week: L:4 T:0 P:0 **Marks:** Internal: **40** External: **60** Total: **100**

End Semester Exam: 3 Hours

Course objectives

- To know the relation between clinical biochemistry and the human body's functioning.
- To understand the basics of life processes and function of the human body in health and disease.
- To integrate the various aspects of metabolism & their regulatory pathways.
- To promote healthy life spans, to promote taking care of each person by themselves and support the maintenance of preventive and therapeutic measures.

Course outcomes (CO's)

1. The students will integrate the knowledge gained on Biochemistry, Anatomy and Physiology, in order to understand the pathophysiology of disease processes and their correlation in the study of body functions.
2. The students will learn how to assess blood test results and their involvement in the assessment of different pathologies.
3. Describe and identify the main characteristics of diagnosis, screening, and prognosis of disease.
4. Apply the processes of scientific research to use in emergency services in clinical biochemistry.

UNIT I: Clinical Samples

Blood collection, processing and transfusion process. Normal blood profile. Cerebrospinal fluid: Composition, clinical investigation of CSF in meningitis. Amniotic fluid: Origin, composition and analysis of amniotic fluid. Collection of urine Urine preservatives. Test for urine compounds. Clinical significance of urinary components.

UNIT II: Serology and Hematology

C- reactive protein test, immunological test for pregnancy. Rheumatoid arthritis (RA) test, ESR. Coagulation test, prothrombin test. Haemoglobin Normal and abnormal Hb, separation of haemoglobin, Thalassemia, Hemoglobinopathies. Disorder of erythrocyte metabolic pathways, erythrocyte enzyme disorders. Porphyrins and disorder: porphyrias.

UNIT III: Clinical Pathology

Myocardial infarctions, hepatobiliary disease. - Enzyme tests in determination of myocardial infarction. Diagnostic enzymes: Principles of diagnostic enzymology. Clinical significance of aspartate aminotransferase, alanine aminotransferase, creatine kinase, aldolase and lactate dehydrogenase. Enzymes of pancreatic origin and biliary tract. Clinical significance of electrolytes. AIDS- Clinical diagnosis. Diagnosis of genetic diseases by molecular biology techniques (cystic fibrosis, Hemachromatosis, thalassemias, sickle cell diseases).

UNIT IV: Oncology

Oncogenes and cell cycle, Etiology-Free radical induced cancer. Free radical scavengers. Antioxidants in disease prevention. Benign and malignant types- Different stages of cancer progression- Cancer Markers. Therapy-Chemotherapy, 4 R's of radiotherapy, Diagnosis and prognosis of various cancers.

UNIT V: Pathophysiology

Pathophysiology of hypothalamus and pituitary (dwarfism, Klienfelter syndrome, adenoma, galactorrhea, amenorrhea). Pathophysiology of thyroid cretinism, myxodema, hashimoto's (autoimmune thyroid disorder), hypo- and hyperparathyroidism, bone (osteopenia and osteoporosis), adrenal (Cushing syndrome and Addison's disease) Pancreas (IDDM and NIDDM) and gonads (cystic ovaries, endometriosis, hypogonadism, cryptorchidis and testicular carcinoma).

SUGGESTED READINGS

1. Murray, R.K., Bender, D.A., Botham, K.M., and Kennelly, P.J., (2012). Harper's illustrated Biochemistry, 29th Edition. McGraw-Hill Medical. London.
2. Chatterjea, M.N., (2011). Text book of medical biochemistry, 8th edition, JB publisher.
3. Burtis, C.A., Ashwood, E.R., and Teitz, W.H., (1999). Textbook of Clinical Biochemistry, W.B. Saunders Company, London.
4. Smith, E., Handler, P., and White, A., (2004). Principles of Biochemistry, Mcgraw Hill International Book Company, London.
5. Varley, H., (2003). Practical Clinical Biochemistry, volume 1 and 2, CBS Publishers, New Delhi.
6. Wards, MJC and Bouchier, I., (1995), Davidson's Principles and Practice of Micine, English Language Book Society.
7. Murray, R.K., Granner, D.K., Mayes, P.A., Rodwell, V.W.,(2012). Harper's illustrated Biochemistry, Appleton and Lange Publishers, London, 29th edition

KARPAGAM ACADEMY OF HIGHER EDUCATION

(Deemed to be University)
(Established Under Section 3 of UGC Act 1956)
Coimbatore - 641021.
(For the candidates admitted from 2017 onwards)
DEPARTMENT OF BIOCHEMISTRTY

SUBJECT : CLINICAL BIOCHEMISTRY

SEMESTER : V
SUBJECT CODE: 17BCU501A CLASS : III B. Sc. BC

LECTURE PLAN
DEPARTMENT OF BIOCHEMISTRTY

S.No	Lecture Duration Hour	Topics to be Covered	Support Material/Page Nos
		UNIT-I	
1	1	Organization of clinical laboratory: Introduction	T1: 2 - 3
2	1	Introduction to instrumentation and automation in clinical biochemistry	T1: 3 - 4
3	1	Safety regulations and first aid in clinical biochemistry	T1: 4 - 5
4	1	Specimen collection, types of specimen for biochemical analysis	T1: 5 - 7
5	1	Precision in clinical laboratory	T1: 9 - 10
6	1	Accuracy in biochemical laboratory	T1: 10 - 15
7	1	Quality control of biochemical laboratory	T1: 28 - 29
8	1	Precautions in biochemical laboratory	T1: 34 - 38
9	1	Limitations of clinical laboratory	T1: 39 - 42
	Total No Of Hours Planned For Unit 1=09		
		UNIT-II	
1	1	Basic hepatic evaluation of biochemical changes in diseases	T1:222-224
2	1	Renal changes occurring during disease conditions	T1:224-226
3	1	Cardiovascular physiology during diseases	T1:34-35
4	1	Biochemical symptoms associated with hepatic and renal diseases	T1:35-38

5	1	Biochemical symptoms associated with cardiovascular diseases	T1:35-36
6	1	Evaluation of hepatic, renal and cardiovascular diseases	T1:36-37
7	1	Diagnostic biochemical profile - I	T1: 39 - 40
8	1	Diagnostic biochemical profile - II	T1: 40 - 42
9	1	Revision of Unit I and II	
	Total No Of Hours Planned For Unit II=09		
		UNIT-III	
1	1	Assessment of glucose metabolism in blood	T1:271-273
2	1	Clinical significance of variations in blood glucose	T1:270-276
3	1	Diabetes mellitus – an Overview	T1:270-271
4	1	Diabetes mellitus - Conditions and clinical symptoms	T1:272-280
5	1	Lipid Profile - Overview	T1:260-261
6	1	Composition of lipoproteins	T1:262-264
7	1	Functions of Lipoprpteins	T1:264-266
8	1	Clinical significance of elevated lipoprotein	T1:266-271
9	1	Revision of Unit III	
	Total No Of Hours Planned For Unit III= 09		
		UNIT-IV	
1	1	Liver function tests — Overview	R1:579-580
2	1	**S**erum enzymes in liver disease	R1:588-590
3	1	Role of SGOT in liver function tests.	R1:589-590
4	1	Role of SGPT in liver function tests.	R1:590-591
5	1	Role of serum phosphatases in liver function tests.	R1:591-592
6	1	Renal function test – Introduction and Clinical significance of GGT	R1:590-591
7	1	Clinical significance of LDH and creatine phosphokinase in kidney function	R1:592-593
8	1	Urine analysis - Physical examination of urine	T1:588-589
9	1	Revision of Unit IV	
	Total No Of Hours Planned For Unit IV=09		

		UNIT-V	
1	1	Test for cardiovascular disease - Overview	T1:280-281
2	1	Role of ECG in cardiovascular disease diagnosis	T1: 283-284
3	1	Involvement of enzymes in diagnostic of heart diseases - Aspartate transaminase	T1:284-286
4	1	Involvement of enzymes in diagnostic of heart diseases - Isoenzymes of creatine kinase	T1: 289-290
5	1	Involvement of enzymes in diagnostic of heart diseases - Lactate dehydrogenase	T1: 290-292
6	1	Involvement of enzymes in diagnostic of heart diseases - troponin	T1: 292-294
7	1	Tumour markers - Overview	T1: 296-297
8	1	Tumour markers for diagnosing various cancers.	T1: 297-304
9	1	Revision of Unit V	
	Total no of Hours Planned for unit V= 09		
Total Planned Hours		**45**	

References:

T1: Medical Laboratory Technology - A Procedure Manual for Routine Diagnostic Tests VoI. II (2010), Mukherjee, K.L., Tata Mc Graw – Hill Publishing Company Ltd. (New Delhi), ISBN: 9780070076648.

R1: Baynes, J.W. and Dominiczak, M.H., (2005). Medical Biochemistry 2nd ed., Elsevier Mosby Ltd. (Philadelphia), ISBN:0-7234-3341-0.

Signature of the Staff

UNIT-I

SYLLABUS

CLINICAL SAMPLES: Blood collection, processing and transfusion process. Normal blood profile. Cerebrospinal fluid: Composition, clinical investigation of CSF in meningitis. Amniotic fluid: Origin, composition and analysis of amniotic fluid. Collection of urine Urine preservatives. Test for urine compounds. Clinical significance of urinary components.

BLOOD COLLECTION, PROCESSING AND TRANSFUSION

Venepuncture using vacutainer needle:

The phlebotomist looks for a suitable vein in front of the elbow: surface veins in the inner elbow (e.g. cephalic, or cubital veins: see below) are preferred for venepuncture, as they lie just below the skin and there are few nerve endings. The participant is asked for their preferred site for the procedure based on their experience.

The participant is seated comfortably in a special phlebotomy chair, which has arm rests and is designed to accommodate a person should they faint during the venepuncture process. The participant‟s arm is placed in a downwards position supported on the arm rest

The phlebotomist gently palpates the selected vein to assess suitability, such as being bouncy, soft, straight, refills when compressed, with a large lumen and well supported. Avoided are veins that are bruised, thin, hard, mobile or near a bony prominence.

A tourniquet is applied to the upper arm on the chosen side (approximately 7 – 10 cm above the intended venepuncture site). The tourniquet is moderately tight, with the radial pulse at wrist still palpable. The tourniquet is in place no longer than one and a half minutes.

The phlebotomist uses one hand to draw skin towards the participant‟s hand so that it is tight over the vein. With the Vacutainer barrel held between thumb and index finger, and needle along the line of the vein at an approximately 15-30 degree angle to skin, the phlebotomist ensures the bevel of the needle is in the upwards position and inserts the needle through skin into the vein

Vacutainer:

A Vacutainer blood collection tube is a sterile glass or plastic test tube with a colored rubber stopper creating a vacuum seal inside of the tube, facilitating the drawing of a predetermined volume of liquid. Vacutainer tubes may contain additives designed to stabilize and preserve the specimen prior to analytical testing. Tubes are available with a safety-engineered stopper, with a variety of labeling options and draw volumes. The color of the top indicates the additives in the vial.

Order of collection	Tube	Tube Volume	Lid colour	Remarks
1.	Blood (EDTA)	10 ml	Purple	Complete blood counts
2.	Blood (Li-Hep - PST) Plasma Separator Tube	10 ml	Green	Urea and electrolyte determination
3.	Blood (Rapid Clot activator Thrombin – SST) Serum Separator Tube STAT SERUM TESTING	10 ml	Orange	Test results that are urgently needed for the diagnosis or treatment of the patient. The delay can be life threatening
4.	Blood (EDTA)	10 ml	Grey	Glucose
5.	Blood (Acid citrate dextrose – 6 ml)	6 ml	Pale Yellow	Test results that are urgently needed for the diagnosis or treatment of the patient. The delay can be life threatening
6.	Blood RNA	3 ml	Blue	Sodium citrate. Citrate is a reversible anticoagulant, and these tubes are used for coagulation assays.

Blood Profile:

Blood is a body fluid in humans and other animals that delivers necessary substances such as nutrients and oxygen to the cells and transports metabolic waste products away from those same cells.

Blood performs many important functions within the body, including:

- Supply of oxygen to tissues (bound to hemoglobin, which is carried in red cells)
- Supply of nutrients such as glucose, amino acids, and fatty acids (dissolved in the blood or bound to plasma proteins (e.g., blood lipids))
- Removal of waste such as carbon dioxide, urea, and lactic acid
- Immunological functions, including circulation of white blood cells, and detection of foreign material by antibodies
- Coagulation, the response to a broken blood vessel, the conversion of blood from a liquid to a semisolid gel to stop bleeding
- Messenger functions, including the transport of hormones and the signaling of tissue damage
- Regulation of core body temperature
- Hydraulic functions

Blood accounts for 7% of the human body weight, with an average density around 1060 kg/m3, very close to pure water's density of 1000 kg/m3. The average adult has a blood volume of roughly 5 litres (11 US pt), which is composed of plasma and several kinds of cells. These blood cells (which are also called corpuscles or "formed elements") consist of erythrocytes (red blood cells, RBCs), leukocytes (white blood cells), and thrombocytes (platelets). By volume, the red blood cells constitute about 45% of whole blood, the plasma about 54.3%, and white cells about 0.7%.

Whole blood (plasma and cells) exhibits non-Newtonian fluid dynamics. If all human hemoglobin were free in the plasma rather than being contained in RBCs, the circulatory fluid would be too viscous for the cardiovascular system to function effectively.

Cells:

One ml of blood contains 4.7 to 6.1 million (male), 4.2 to 5.4 million (female) erythrocytes: Red blood cells contain the blood's hemoglobin and distribute oxygen. Mature red blood cells lack a nucleus and organelles in mammals. The red blood cells (together with endothelial vessel cells and other cells) are also marked by glycoproteins that define the different blood types. The proportion of blood occupied by red blood cells is referred to as the hematocrit, and is normally about 45%. The combined surface area of all red blood cells of the human body would be roughly 2,000 times as great as the body's exterior surface.

4,000–11,000 leukocytes: White blood cells are part of the body's immune system; they destroy and remove old or aberrant cells and cellular debris, as well as attack infectious agents (pathogens) and foreign substances. The cancer of leukocytes is called leukemia.

200,000–500,000 thrombocytes: Also called platelets, they take part in blood clotting (coagulation). Fibrin from the coagulation cascade creates a mesh over the platelet plug.

Plasma:

About 55% of blood is blood plasma, a fluid that is the blood's liquid medium, which by itself is straw-yellow in color. The blood plasma volume totals of 2.7–3.0 liters (2.8–3.2 quarts) in an average human. It is essentially an aqueous solution containing 92% water, 8% blood plasma proteins, and trace amounts of other materials. Plasma circulates dissolved nutrients, such as

glucose, amino acids, and fatty acids (dissolved in the blood or bound to plasma proteins), and removes waste products, such as carbon dioxide, urea, and lactic acid.

Other important components include:

- Serum albumin
- Blood-clotting factors (to facilitate coagulation)
- Immunoglobulins (antibodies)
- lipoprotein particles
- Various other proteins
- Various electrolytes (mainly sodium and chloride)

The term serum refers to plasma from which the clotting proteins have been removed. Most of the proteins remaining are albumin and immunoglobulins.

Constitution of normal blood

Parameter	Value
Hematocrit	45 ± 7 (38–52%) for males 42 ± 5 (37–47%) for females
pH	7.35–7.45
base excess	−3 to +3
PO_2	10–13 kPa (80–100 mm Hg)
PCO_2	4.8–5.8 kPa (35–45 mm Hg)
HCO_3^-	21–27 mM
Oxygen saturation	Oxygenated: 98–99% Deoxygenated: 75%

Cerebrospinal Fluid

The surface of the central nervous system is covered by the meninges, three layers called as the piamater, arachnoid mater and duramater. The last is the outermost layer. CSF is found between the pia and the arachnoid, i.e. sub-arachnoid space and is formed by _active' secretion from the cells of the choroid plexuses, the vascular structures lying within the ventricles of the brain. It is not just a plasma ultrafiltrate. In normal healthy adults, the rate of formation of CSF is 100 to 250 ml per 24 hours and total volume of CSF is approx 100 to 200 ml. In addition to the cell count, microbiological and serological tests, the chemical tests that are commonly and routinely carried out on CSF are protein and glucose estimations, chloride tests are rarely done now.

Site of withdrawal: The chemical composition of CSF from a normal subject depends on the site of withdrawal, ventricular and lumbar CSF differ from each other in certain respects, which will be discussed under the various constituents. Generally only lumbar CSF is examined. The spinal cord ends near the 1st lumbar vertebra and the accumulation of fluid below this, called as lumbar fluid, is the portion of CSF commonly subjected for analysis. It is obtained by passing a lumbar puncture needle, aseptically, between the 3rd and 4th lumbar vertebrae into the subarachnoid space. ―Blood-Brain‖ Barrier ―A blood CSF barrier‖ exists for many substances including the blood constituents, drugs, enzymes, etc. and their concentration in CSF is lower than in plasma. In inflammatory states and in cerebrovascular accidents, the blood-CSF barrier may be impaired and the differences may be less marked.

COMPOSITION OF NORMAL CSF (LUMBAR FLUID)

Colour and appearance	:	Clear, colourless, no coagulum or deposit.
Pressure	:	60 to 150 mm CSF
Specific gravity	:	1.006 to 1.007
Cells	:	0 to 4 mononuclear cells per C. mm
pH	:	7.3 (anaerobically)
Protein content	:	10 to 45 mg per 100 ml
Globulins (Qualitative)	:	Not increased. Pandy's test and Nonne-Apelt tests-negative
Glucose	:	45 to 100 mg per 100 ml
Chlorides	:	700 to 760 mg per 100 ml as NaCl (120 to 130 mEq per litre)
Urea	:	20 to 40 mg per 100 ml
Calcium	:	5.5 to 6 mg per 100 ml

Comparison of Average Serum and Cerebrospinal Fluid

Substance	CSF	Serum
Water Content (%)	99	93
Protein (mg/dL)	35	7000
Glucose (mg/dL)	60	90
Osmolarity (mOsm/L)	295	295
Sodium (mEq/L)	138	138
Potassium (mEq/L)	2.8	4.5
Calcium (mEq/L)	2.1	4.8
Magnesium (mEq/L)	2.0–2.5	1.7
Chloride (mEq/L)	119	102
pH	7.33	7.41

Table 42.1: Cerebrospinal fluid findings in CNS diseases

Disease	Appearance	Cells	Protein: Qualitative	Protein: Quantitative mg%	Glucose mg%	Chlorides mg%	Lange's colloidal reaction	Remarks
Normal	Clear, colourless no clot	0-4 mononuclears per C. mm	0	10-15	45 to 100	700-760	0	—
(a) Acute Meningitis								
1. Pyogenic meningitis	Turbid may be thick clot	100 to 6000 95% polymorphs	++ to ++++	Markedly increased (1.0 to 10.0 g/l)	0 to 15 or absent	630 to 680	Meningitic	Coccican be seen in smear or culture
2. Tuberculous meningitis	Clear, opalescent or white 'cob-web' clot on standing	Children early 10-100 Late: 100 to 1000 70 to 90% Lymphocytes, poly ±	± to +++	30 to 400 Highest shortly before death	15 to 20	Early 680-700 Late: 500-630	Weak Meningitic	M tuberculosis from clot
3. Pneumococcal meningitis	Turbid to yellow clots	Acute cases slight increase. Less acute cases 100 to 5000 95% polymorphs	++ to ++++	100 to 200 mg% or higher	0 to 10	600 to 650	Meningitic	Pneumococci in smear and culture
4. Syphilitic meningitis	Clear to turbid may be fibrin clot	10-500 90% mononuclears (Lymphocytes)	±	25 to 60 mg%	Usually Normal	650 to 720	Luetic or paretic	—
Viral Meningitis	Clear or sometimes opaque	Early: 10-100 Late: 100-500 Lymphocytes ++	+	45-100	Normal	Normal	Normal	—
Meningism in acute fever	Clear	Slight increase Lymphocytes +	—	15-50	Normal	Normal	Normal	—
(b) Epidemic Encephalitis	Clear Occasional fibrin clot	10 to 200 All monocytes Less than 10 in 30 to 50% cases	±	25-60	Above Normal 65-120	Normal or increased	Paretic or Meningitic	—
(c) Acute Poliomyelitis	Clear to milky Occasional fibrin clot	Pre-paralytic 15 to 2000 polys Paralytic 10 to 100 mononuclears	± to ++	Pre-paralytic 25 to 60 paralytic 60-300	Normal	Normal	Variable	—
(d) Cerebral Tumour	Normal or Xanthochromic	Normal or 10-80	± to ++	50-200	40-100	Normal	Variable	High protein in acoustic neurona and meningiomas
(e) Spinal Block (Froin's syndrome)	Opalescent with clot ++	Normal or slight increase	+ to +++	50-100	Normal	Normal	Variable or Meningitic	—
(f) Multiple Sclerosis	Normal	70 to 90% cases normal, others 5-50 (Lympho)	0 to +	30 to 90 mg% 10 to 40% of cases above normal Increase in γ-globulins	Normal	Normal	50-60% paretic curve	'Oligoclonal' γ-globulin (weak paretic)

Functions of CSF:

CSF serves several purposes:

Buoyancy: The actual mass of the human brain is about 1400–1500 grams; however, the net weight of the brain suspended in CSF is equivalent to a mass of 25-50 grams. The brain therefore exists in neutral buoyancy, which allows the brain to maintain its density without being impaired by its own weight, which would cut off blood supply and kill neurons in the lower sections without CSF.

Protection: CSF protects the brain tissue from injury when jolted or hit, by providing a fluid buffer that acts as a shock absorber from some forms of mechanical injury.

Prevention of brain ischemia: The prevention of brain ischemia is made by decreasing the amount of CSF in the limited space inside the skull. This decreases total intracranial pressure and facilitates blood perfusion.

Homeostasis: CSF allows for regulation of the distribution of substances between cells of the brain, and neuroendocrine factors, to which slight changes can cause problems or damage to the nervous system. For example, high glycine concentration disrupts temperature and blood pressure control, and high CSF pH causes dizziness and syncope.

Clearing waste: CSF allows for the removal of waste products from the brain, and is critical in the brain's lymphatic system. Metabolic waste products diffuse rapidly into CSF and are removed into the bloodstream as CSF is absorbed.

Amniotic fluid

The amniotic fluid is the protective liquid contained by the amniotic sac of a gravid Amniote. This fluid serves as a cushion for the growing fetus, but also serves to facilitate the exchange of

nutrients, water, and biochemical products between mother and fetus.

Development

Amniotic fluid is present from the formation of the gestational sac. Amniotic fluid is in the amniotic sac. It is generated from maternal plasma, and passes through the fetal membranes by osmotic and hydrostatic forces. When fetal kidneys begin to function in about week 16, fetal urine also contributes to the fluid. In earlier times, it was believed that the amniotic fluid was composed entirely of fetal urine.

Contents

At first, amniotic fluid is mainly water with electrolytes, but by about the 12-14th week the liquid also contains proteins, carbohydrates, lipids and phospholipids, and urea, all of which aid in the growth of the fetus.

Volume

The volume of amniotic fluid increases with the growth of fetus. From the 10th to the 20th week it increases from 25ml to 400ml approximately. Approximately in the 10th-11th week the breathing and swallowing of the fetus slightly decrease the amount of fluid, but neither urination nor swallowing contributes significantly to fluid quantity changes, until the 25th week, when keratinization of skin is complete. Then the relationship between fluid and fetal growth stops. It reaches a plateau of 800ml by the 28-week gestational age. The amount of fluid declines to roughly 400 ml at 42 weeks. There is about 1L of amniotic fluid at birth

Function

Swallowed amniotic fluid creates urine and contributes to the formation of meconium. Amniotic fluid protects the developing baby by cushioning against blows to the mother's abdomen, allowing for easier fetal movement and promoting muscular/skeletal development. Amniotic

fluid swallowed by the fetus helps in the formation of the gastrointestinal tract. Contrary to popular belief, amniotic fluid has not been conclusively shown to be inhaled and exhaled by the fetus. Lung development occurs as a result of the production of fetal lung fluid which expands the lungs. It also prevents the fetus from mechanical jerks and shocks.

Clinical significance Collection

Amniotic fluid is removed from the mother by an amniocentesis procedure, where a long needle is inserted through the abdomen into the amniotic sac, using ultrasound guidance such that the fetus is not harmed. Amniocentesis is an abnormal procedure, and is only performed if there is a suspicion of health defects in the fetus, or if an early delivery of the fetus may be necessary, since there can be complications from the procedure. If warranted, fluid is collected between 16–42 weeks of fetal development, and 20-30ml of fluid are removed.

Analysis

Analysis of amniotic fluid can reveal many aspects of the baby's genetic health as well as the age and viability of the fetus. This is because the fluid contains metabolic wastes and compounds used in assessing fetal age and lung maturity, but amniotic fluid also contains fetal cells, which can be examined for genetic defects.

Amniotic fluid normally has a pH of 7.0 to 7.5. Because pH in the upper vagina is normally acidic (pH 3.8-4.5), a vaginal pH test showing a pH of more than 4.5 strengthens a suspicion of rupture of membranes in case of clear vaginal discharge in pregnancy. Other tests for detecting amniotic fluid mainly include nitrazine paper test and fern test. One main test that is performed on amniotic fluid is the L/S ratio test (lecithin/sphigomyelin). This test is used to determine fetal lung maturity. Both lecithin and sphingomyelin are lung surfactants that are present in increasing amounts in the maturing fetus, though past week 33, sphigomyelin levels remain relatively constant. Measuring a ratio of L/S of 2:1 or greater indicates that the fetus can be safely delivered, with functioning lungs.

Complications related to amniotic fluid

Too little amniotic fluid (oligohydramnios) can be a cause or an indicator of problems for the mother and baby. The majority of pregnancies proceed normally and the baby is born healthy, but this isn't always the case. Babies with too little amniotic fluid can develop contractures of the limbs, clubbing of the feet and hands, and also develop a life-threatening condition called hypoplastic lungs. If a baby is born with hypoplastic lungs, which are small underdeveloped lungs, this condition is potentially fatal and the baby can die shortly after birth due to inadequate oxygenation. Potter sequence refers to a constellation of findings related to insufficient amniotic fluid and includes shortened and malformed limbs with clubbed feet and the underdeveloped lungs that can lead to perinatal death.

On every prenatal visit, the obstetrician/gynaecologist or midwife should measure the patient's fundal height with a tape measure. It is important that the fundal height be measured and properly recorded to track proper fetal growth and the increasing development of amniotic fluid. The obstetrician/gynaecologist or midwife should also routinely ultrasound the patient—this procedure will also give an indication of proper fetal growth and amniotic fluid development. Oligohydramnios can be caused by infection, kidney dysfunction or malformation (since much of the late amniotic fluid volume is urine), procedures such as chorionic villus sampling (CVS), and preterm premature rupture of membranes (PPROM). Oligohydramnios can sometimes be treated with bed rest, oral and intravenous hydration, antibiotics, steroids, and amnioinfusion.[citation needed] It is also important to keep the baby warm and moist.

The opposite of oligohydramnios is polyhydramnios, an excess volume of amniotic fluid in the amniotic sac. A rare but very often fatal condition (fatal for both mother and child) connected with amniotic fluid is amniotic fluid embolism.

Stem cell research

Main article: Amniotic stem cells

Recent studies show that amniotic fluid contains a considerable quantity of stem cells. These

amniotic stem cells are pluripotent and able to differentiate into various tissues, which may be useful for future human application. Some researchers have found that amniotic fluid is also a plentiful source of non-embryonic stem cells. These cells have demonstrated the ability to differentiate into a number of different cell-types, including brain, liver and bone. It is possible to conserve the stem cells extracted from amniotic fluid in private stem cells banks.

URINALYSIS

I. LEARNING OBJECTIVES

1. Understand the basic principles of urine collection.

2. Describe the different types of urinalysis and understand their corresponding clinical-pathological correlation:

a. Macroscopic examination

b. Chemical analysis: Use and interpretation of dipstick

i. Glucose

ii. Bilirubin

iii. Ketones

iv. Specific gravity

v. Blood

vi. pH

vii. Protein

viii. Urobilinogen

ix. Nitrite

x. Leukocyte esterase

c. Microscopic Examination

d. Cytology

3. Interpret some of the most common chemical and cytological changes in urine samples in the most common inflammatory and neoplastic diseases of the kidney and the urinary tract.

II. INTRODUCTION: Urinalysis is a physical and/or chemical examination of the urine. It consists of a battery of chemical and microscopic tests to screen for urinary tract infections, renal disease, and diseases of other organs that result in the appearance of abnormal metabolites (break-down products) in the urine. Urinalysis can reveal diseases that have gone unnoticed because they do not produce striking signs or symptoms. Examples include diabetes mellitus, various forms of glomerulonephritis, and chronic urinary tract infections. In other urinary diseases with symptoms, a urinalysis can help to confirm of rule out some diseases.

III. SPECIMEN COLLECTION: A "clean-catch" urine sample is performed by collecting the sample of urine in midstream. Men or boys should wipe clean the head of the penis. Women or girls need to wash the area between the lips of the vagina with soapy water and rinse well. A small amount of urine should initially fall into the toilet bowl before it is collected (this clears the urethra of contaminants). Then, in a clean container (properly labeled with the name of the patient and date), catch about 1 to 2 ounces of urine and remove the container from the urine stream.

For an infant, thoroughly wash the area around the urethra. Open a urine collection bag (a plastic bag with an adhesive paper on one end), and place it on the genital area. For males, the entire penis can be placed in the bag and the adhesive attached to the skin. For females, the bag is placed over the labia majora. Place a diaper, check the infant frequently and remove the bag after the infant has urinated into it. The urine is then drained into a labeled container.

IV. METHODS OF URINE COLLECTION

1. Random collection taken at any time of day with no precautions regarding contamination. The sample may be dilute, isotonic, or hypertonic and may contain white cells, bacteria, and squamous epithelium as contaminants. In females, the specimen may cont contain vaginal contaminants such as trichomonads, yeast, and during menses, red cells.

2. Early morning collection of the sample before ingestion of any fluid. This is usually hypertonic and reflects the ability of the kidney to concentrate urine during dehydration which occurs overnight. If all fluid ingestion has been avoided since 6 p.m. the previous day, the specific gravity usually exceeds 1.022 in healthy individuals.

3. Clean-catch, midstream urine specimen collected after cleansing the external urethral meatus. A cotton sponge soaked with benzalkonium hydrochloride is useful and non- irritating for this purpose. A midstream urine is one in which the first half of the bladder urine is discarded and the collection vessel is introduced into the urinary stream to catch the last half. The first half of the stream serves to flush contaminating cells and microbes from the outer urethra prior to collection. This sounds easy, but it isn't (try it yourself before criticizing the patient).

4. Catherization of the bladder through the urethra for urine collection is carried out only in special circumstances, i.e., in a comatose or confused patient. This procedure risks introducing infection and traumatizing the urethra and bladder, producing iatrogenic infection or hematuria.

5. Suprapubic needle aspiration of the bladder. When done under ideal conditions, this provides the purest sampling of bladder urine. This is a good method for infants and small children.

V. TYPES OF URINALYSIS

- Macroscopic Examination
- Chemical Analysis (Urine Dipstick)
- Microscopic Examination
- Culture (not covered on this lecture))
- Cytological Examination

VI. MACROSCOPIC EXAMINATION

The first part of a urinalysis is direct visual observation. Normal, fresh urine is pale to dark

yellow or amber in color and clear. Normal urine volume is 750 to 2000 ml/24hr.

Odor:

- Ammonia-like: (Urea-splitting bacteria)
- Foul, offensive: Old specimen, pus or inflammation
- Sweet: Glucose
- Fruity: Ketones
- Maple syrup-like: (Maple Syrup Urine Disease) Color:
- Colorless: Diluted urine
- Deep Yellow: Concentrated Urine, Riboflavin
- Yellow-Green: Bilirubin / Biliverdin
- Red: Blood / Hemoglobin
- Brownish-red : Acidified Blood (Actute GN)
- Brownish-black: Homogentisic acid (Melanin) Turbidity:
- Typically cells or crystals. Crystals develop from crystallization or precipitation of salts upon standing at room temperature or in the refrigerator.
- Cellular elements and bacteria will clear by centrifugation.
- Crystals dissolved by a variety of methods.
- Microscopic examination will determine which is present.

Clearing of the specimen after addition of a small amount of acid indicates that precipitation of salts is the probable cause of turbidity. A red or red-brown (abnormal) color could be from a food dye, eating fresh beets, a drug, or the presence of either hemoglobin or myoglobin. If the sample contained many red blood cells, it would be cloudy as well as red.

VII. CHEMICAL ANALYSIS (URINE DIPSTICK)

The state-of-the-art technology is the use of dipstick to detect biochemical substances in urine in a convenient way. Many companies are now manufacturing test strips based on the basic wet

chemistry reactions of the respective biochemical substances. This microchemistry system has been available for many years and allows qualitative and semi-quantitative analysis within one minute by simple but careful observation. The color change occurring on each segment of the strip is compared to a color chart to obtain results. However, a careless examination may lead to misreading or misinterpreting the results.

Procedure: Follow the instructions provided in the kit, insert the strip carefully and handle it by the end which is away from the reagent area. Completely immerse the reagent area fresh urine for 1-2 seconds and remove. Gently tap the edge of the strip against the side of the urine container to remove excess urine. After the time indicated for each analyte, hold the strip close to the color chart, match carefully and compare the test areas with the reference chart.

Results: The results are expressed as either negative or varying degrees of positive, indicating different amounts of the specific analyte present.

Storage: Protect the strips from moisture and excessive heat and light but do not refrigerate. Replace the top on the storage container immediately after removing a strip. Exposure to atmospheric air reduces the sensitivity. Darkening of the enzyme-coated area indicates loss of sensitivity. Hence discolored strips should not be used.

Glucose

Compared to Benedict‘s test, the dipstick strip tests detect semi-quantitatively the amount of glucose present in urine. These are fast and convenient ways of testing urine to determine the amount of glucose excreted in urine. Less than 0.1% of glucose normally filtered by the glomerulus appears in urine (< 130 mg/24 hr). Glycosuria (excess sugar in urine) generally means diabetes mellitus. The strip has an area impregnated with the enzymes glucose oxidase and peroxides, together with potassium iodide and a blue background dye. The oxygen liberated

in the final reaction binds with the dye to produce a series of color changes 30 seconds after wetting the strip with urine. The color is then compared with the standard chart provided in the kit to report the approximate level of glucose present in the urine. As ascorbic acid is an oxygen acceptor and most likely to be present in large amounts in the urine of pregnant women, this will cause a false-negative result. Dipsticks employing the glucose oxidase reaction for screening are specific for glucose but can miss other reducing sugars such as galactose and fructose. For this reason, most newborn and infant urines are routinely screened for reducing sugars by methods other than glucose oxidase (such as the Clinitest, a modified Benedict's copper reduction test).

Bilirubin

It is based on the coupling of bilirubin with diazotized dichloronaniline in a strongly acid medium. The color ranges through various shades of tan. Indican (ureloxylsulfate) will cause a false-positive result, while ascorbate will cause a false-negative result. Increased direct bilirubin (correlates with urobilinogen and serum bilirubin). Interference is produced by prolonged exposure of sample to light. The test measures direct bilirubin only, it will not pick up indirect bilirubin. Other tests that can be used are Ictotest (more sensitive tablet version of same assay) and serum test for total and direct bilirubin, which is more informative

Ketones

Ketones resulting from either diabetic ketosis or some other form of calorie deprivation (starvation) are easily detected using dipsticks containing sodium nitroprusside. It is based on Rothera's reaction principle and on the development of colors, ranging from buff-pink for a negative reading to purple when acetoacetate reacts with nitropruside. It also detects acetone but not beta-hydroxybutyrate. Interference can be produced by the use of expired reagents (degradation with exposure to moisture in air). The test only measures acetoacetate but no other ketone bodies such as beta-hydroxybutyric acid (Rebound Ketosis). Other Tests more sensitive

are Ketostix (more sensitive tablet version of same assay) and serum glucose measurement to confirm Diabetic ketoacidosis.

Specific Gravity

Urine specific gravity (SG) is based on the ratio of weight of urine to weight of an equivalent volume of pure water. This test is used to measure tubular function. SG measures urine density, or the ability of the kidney to concentrate or dilute the urine over that of plasma. The dipstick measures SG by measuring the change in pKa of polyelectrolytes in relation to ionic concentration. Although dipstick strips do have a method of approximating specific gravity, this measurement is best made with a refractometer. SG between 1.002 and 1.035 on a random sample should be considered normal if kidney function is normal. Since the SG of the glomerular filtrate in Bowman‘s space ranges from 1.007 to 1.010, any measurement below this range indicates hydration and any measurement above it indicates relative dehydration. If SG is not > 1.022 after a 12 hour period without food or water, renal concentrating ability is impaired and the patient either has generalized renal impairment or nephrogenic diabetes insipidus. In end-stage renal disease, SG tends to become 1.007 to 1.010. Any urine having a SG over 1.035 is either contaminated contains very high levels of glucose, or the patient may have recently received high density radiopaque dyes intravenously for radiographic studies or low molecular weight dextran solutions. Subtract 0.004 for every 1% of glucose to determine non-glucose solute concentration.

Blood

The occult blood test will react positively in the presence of red blood cells, free hemoglobin or free myoglobin. Hemoglobin usually is bound and is too large to pass through the glomerular filter. If the renal threshold is exceeded, the hemoglobin can pass into the urine. Myoglobin on the other hand, is not bound and freely passes through the glomerular filter. Myoglobin can be

detected in urine before a change in plasma color is apparent. The presence of free red blood cells results in a positive test when blood cells lyse and hemoglobin is released. Healthy individuals should have negative test results.

This test is based on a pseudoperoxidase reaction, which is more sensitive to hemoglobin and myoglobin than intact red blood cells. A positive occult blood test indicates hematuria, hemoglobinuria, or myoglobinuria. Further evaluation of the urine sediment is needed if a positive test result is found. Most commonly, hematuria is the cause of the positive test result while myoglobinuria is rare. Hematuria can be caused by trauma, infection, inflammation, infarction, calculi, neoplasia or a coagulopathy anywhere along the urinary tract. In cases of hematuria, the urine is red and cloudy, but will clear if centrifuged. Microscopic evaluation of the urine sediment will reveal red blood cells.

Hemoglobinuria, on the other hand, will have reddish brown urine that does not become clear after centrifugation. The microscopic evaluation of urine sediment will not reveal red blood cells. With intravascular hemolysis, plasma will have a reddish tint due to hemoglobinemia that is detectable prior to hemoglobinuria. The patient usually will be clinically anemic. A false positive test result may occur if the urine is contaminated with bleach, or contains large amounts of iodide or bromide. If a voided sample is collected from a woman during a menstrual period, a false positive test may also occur. False negative test results may occur if the urine is not well mixed prior to evaluation. This is due to the fact that red blood cells often sediment quickly.

pH

The glomerular filtrate of blood plasma is usually acidified by renal tubules and collecting ducts from a pH of 7.4 to about 6 in the final urine. However, depending on the acid-base status, urinary pH may range from as low as 4.5 to as high as 8.0. The change to the acid side of 7.4 is accomplished in the distal convoluted tubule and the collecting duct. Acidic urine (less than 4.5)

is present in metabolic acidosis and high-protein diet. Alkaline urine (greater than 8.0) is present in renal tubular acidosis (>5.5). Interference of the test is produced by bacterial overgrowth (alkaline or acidic), ―run over effect‖ effect of protein pad on pH indicator pad. Buffers from the protein area of the strip (pH 3.0) spill over to the pH area of the strip and make the pH of the sample appear more acidic than it really is. Other Tests to perform are titrable acidity and blood gases to determine acid-base status.

Protein

Dipstick screening for protein is done on whole urine, but semi-quantitative tests for urine protein should be performed on the supernatant of centrifuged urine since the cells suspended in normal urine can produce a falsely high estimation of protein. Normally, only small plasma proteins filtered at the glomerulus are reabsorbed by the renal tubule. However, a small amount of filtered plasma proteins and protein secreted by the nephron (Tamm-Horsfall protein) can be found in normal urine. Normal total protein excretion does not usually exceed 150 mg/24 hours or 10 mg/100 ml in any single specimen. More than 150 mg/day is defined as proteinuria. Proteinuria > 3.5 gm/24 hours is severe and known as nephrotic syndrome.

The majority of the test strips has been developed to detect albumin and may be negative in the presence of globulins and Bence Jones Proteins. Dipsticks detect protein by production of color with an indicator dye, Bromphenol blue, which is most sensitive to albumin. Precipitation by heat is a better semiquantitative method, but overall, it is not a highly sensitive test. The sulfosalicylic acid test is a more sensitive precipitation test. It can detect albumin, globulins, and Bence-Jones protein at low concentrations. In rough terms, trace positive results (which represent a slightly hazy appearance in urine) are equivalent to 10 mg/100 ml or about 150 mg/24 hours (the upper limit of normal). 1+ corresponds to about 200-500 mg/24 hours, a 2+ to 0.5-1.5 gm/24 hours, a 3+ to 2-5 gm/24 hours, and a 4+ represents 7 gm/24 hours or greater. A false-positive result may occur if the specimen is contaminated with vaginal or urethral secretions, when

strongly alkaline urine is used, and when the urine container is contaminated with disinfectants such as chlorohexidine. False- negative results will be observed if acid has been added to the urine as a preservative (for example for the estimation of urinary calcium).

Urobilinogen

Urobilinogen is formed by intestinal bacteria from the breakdown of conjugated bilirubin, and it is usually excreted in feces. However a small amount may be reabsorbed and excreted in urine. This test is based on a modified Ehrlich reaction, in which p-dimethyl amino benzaldehyde in conjunction with a color enhancer reacts with urobilinogen in a strongly acid medium to produce a pink-red color. A positive test response indicates normal enterohepatic circulation of biliary pigments. High concentrations of biliary pigments may occur in hemolytic crisis, or cases of hepatic or intestinal dysfunction. A false positive test result may occur if the temperature of the reagent strip is elevated. A false negative test result may occur if there is formalin residue in the collection container, or if the sample is old, because urobilinogen is very unstable when exposed to light and air.

Nitrite

A positive nitrite test indicates that bacteria may be present in significant numbers in urine. Interference is produced by : bacterial overgrowth. The test is only able to detect bacteria that reduce nitrate to nitrite. Gram negative rods such as E. coli are more likely to give a positive test. Correlate a positive nitrite test with leukocyte esterase. Other tests to be performed are urine microscopic examination (bacteria and leukocytes) and urine culture.

Leukocyte Esterase

A positive leukocyte esterase test results from the presence of white blood cells either as whole

cells or as lysed cells. Pyuria can be detected even if the urine sample contains damaged or lysed WBC's. A negative leukocyte esterase test means that an infection is unlikely and that, without additional evidence of urinary tract infection, microscopic exam and/or urine culture need not be done to rule out significant bacteriuria. Leukocytes are measured by a reaction of the esterases in leukocytes that catalyze reaction of pyrrole amino acid ester to release 3-hydroxy-5-phenol pyrrole. False positive test results also may occur in the event of vaginal contamination. False negative test results may develop if the patient has been treated with high doses of antibiotics. Glucosuria or increased urine specific gravity may cause false negative test results.

VIII. MICROSCOPIC EXAMINATION General Aspects

Preservation:

- Cells and casts begin to disintegrate in 1 - 3 hrs. at room temp.
- Refrigeration for up to 48 hours (little loss of cells).

Specimen concentration: Ten to twenty-fold concentration by centrifugation. Types of microscopy:

- Phase contrast microscopy
- Polarized microscopy
- Bright field microscopy with special staining (e.g., Sternheimer-Malbin stain)

Methodology

A sample of well-mixed urine (usually 10-15 ml) is centrifuged in a test tube at relatively low speed (about 2-3,000 rpm) for 5-10 minutes until a moderately cohesive button is produced at the bottom of the tube. The supernate is decanted and a volume of 0.2 to 0.5 ml is left inside the tube. The sediment is resuspended in the remaining supernate by flicking the bottom of the tube several times. A drop of resuspended sediment is poured onto a glass slide and cover slipped.

Examination

The sediment is first examined under low power to identify most crystals, casts, squamous cells, and other large objects. The numbers of casts seen are usually reported as number of each type found per low power field (LPF). Example: 5-10 hyaline casts/L casts/LPF. Since the number of elements found in each field may vary considerably from one field to another, several fields are averaged. Next, examination is carried out at high power to identify crystals, cells, and bacteria. The various types of cells are usually described as the number of each type found per average high power field (HPF). Example: 1-5 WBC/HPF.

Abnormal Findings:

Per High Power Field (HPF) (400x):

> 3 erythrocytes
> 5 leukocytes
> 2 renal tubular cells
> 10 bacteria

Per Low Power Field (LPF) (200x):

> 3 hyaline casts or > 1 granular cast
> 10 squamous cells (indicative of contaminated specimen) Any other cast (RBCs, WBCs)

Presence of:

Fungal hyphae or yeast, parasite, viral inclusions

Pathological crystals (leucine, tyrosine, cystine) Large number of uric acid or calcium oxalate crystals

Red Blood Cells

Hematuria is the presence of abnormal numbers of red cells in urine due to: glomerular damage, tumors which erode the urinary tract anywhere along its length, kidney trauma, urinary tract stones, renal infarcts, acute tubular necrosis, upper and lower uri urinary tract infections, nephrotoxins, and physical stress.

Red cells may also contaminate the urine from the vagina in menstruating women or from trauma produced by bladder catherization. Theoretically, no red cells should be found, but some find their way into the urine even in very healthy individuals. However, if one or more red cells can be found in every high power field, and if contamination can be ruled out, the specimen is probably abnormal.

RBC's may appear normally shaped, swollen by dilute urine (in fact, only cell ghosts and free hemoglobin may remain), or crenated by concentrated urine. Both swollen, partly hemolyzed RBC's and crenated RBC's are sometimes difficult to distinguish from WBC's in the urine. In addition, red cell ghosts may simulate yeast. The presence of dysmorphic RBC's in urine suggests a glomerular disease such as a glomerulonephritis. Dysmorphic RBC's have odd shapes as a consequence of being distorted via passage through the abnormal glomerular structure.

White Blood Cells

Pyuria refers to the presence of abnormal numbers of leukocytes that may appear with infection in either the upper or lower urinary tract or with acute glomerulonephritis. Usually, the WBC's are granulocytes. White cells from the vagina, especially in the presence of vaginal and cervical infections, or the external urethral meatus in men and women may contaminate the urine. If two or more leukocytes per each high power field appear in non- contaminated urine, the specimen is probably abnormal. Leukocytes have lobed nuclei and granular cytoplasm.

Epithelial Cells

Renal tubular epithelial cells, usually larger than granulocytes, contain a large round or oval nucleus and normally slough into the urine in small numbers. However, with nephrotic syndrome and in conditions leading to tubular degeneration, the number sloughed is increased. When lipiduria occurs, these cells contain endogenous fats. When filled with numerous fat droplets, such cells are called oval fat bodies. Oval fat bodies exhibit a "Maltese cross" configuration by polarized light microscopy.

Transitional epithelial cells from the renal pelvis, ureter, or bladder have more regular cell borders, larger nuclei, and smaller overall size than squamous epithelium. Renal tubular epithelial cells are smaller and rounder than transitional epithelium, and their nucleus occupies more of the total cell volume. Squamous epithelial cells from the skin surface or from the outer urethra can appear in urine. Their significance is that they represent possible contamination of the specimen with skin flora.

Casts

Urinary casts are formed only in the distal convoluted tubule (DCT) or the collecting duct (distal nephron). The proximal convoluted tubule (PCT) and loop of Henle are not locations for cast formation. Hyaline casts are composed primarily of a mucoprotein (Tamm-Horsfall protein) secreted by tubule cells. The Tamm-Horsfall protein secretion, forms hyaline casts in the distal collecting duct. Even with glomerular injury causing increased glomerular permeability to plasma proteins with resulting proteinuria, most matrix or "glue" that cements urinary casts together is Tamm-Horsfallmucoprotein, although albumin and some globulins are also incorporated.

The factors which favor protein cast formation are low flow rate, high salt concentration, and

low pH, all of which favor protein denaturation and precipitation, particularly that of the Tamm-Horsfall protein. Protein casts with long, thin tails formed at the junction of Henle's loop and the distal convoluted tubule are called cylindroids. Hyaline casts can be seen even in healthy patients**.**

Red blood cells may stick together and form red blood cell casts. Such casts are indicative of glomerulonephritis, with leakage of RBC's from glomeruli, or severe tubular damage. White blood cell casts are most typical for acute pyelonephritis, but they may also be present with glomerulonephritis. Their presence indicates inflammation of the kidney, because such casts will not form except in the kidney.

When cellular casts remain in the nephron for some time before they are flushed into the bladder urine, the cells may degenerate to become a coarsely granular cast, later a finely granular cast, and ultimately, a waxy cast. Granular and waxy casts are be believed to derive from renal tubular cell casts. Broad casts are believed to emanate from damaged and dilated tubules and are therefore seen in end-stage chronic renal disease.

The so-called telescoped urinary sediment is one in which red cells, white cells, oval fat bodies, and all types of casts are found in more or less equal profusion. The conditions which may lead to telescoped sediment are: 1) lupus nephritis 2) malignant hypertension 3) diabetic glomerulosclerosis, and 4) rapidly progressive glomerulonephritis. In end-stage kidney disease of any cause, the urinary sediment often becomes very scant because few remaining nephrons produce dilute urine.

Bacteria

Bacteria are common in urine specimens because of the abundant normal microbial flora of the vagina or external urethral meatus and because of their ability to rapidly multiply in urine

standing at room temperature. Therefore, microbial organisms found in all but the most scrupulously collected urines should be interpreted in view of clinical symptoms. Diagnosis of bacteriuria in a case of suspected urinary tract infection requires culture. A colony count may also be done to see if significant numbers of bacteria are present. Generally, more than 100,000/ml of one organism reflects significant bacteriuria. Multiple organisms reflect contamination. However, the presence of any organism in catheterized or suprapubic tap specimens should be considered significant.

Yeasts

Yeast cells may be contaminants or represent a true yeast infection. They are often difficult to distinguish from red cells and amorphous crystals but are distinguished by their tendency to bud. Most often they are Candida, which may colonize bladder, urethra, or vagina.

Crystals

Common crystals seen even in healthy patients include calcium oxalate, triple phosphate crystals and amorphous phosphates. Very uncommon crystals include: cystine crystals in urine of neonates with congenital cystinuria or severe liver disease, tyrosine crystals with congenital tyrosinosis or marked liver impairment, or leucine crystals in patients with severe liver disease or with maple syrup urine disease.

Miscellaneous

General artifacts or unidentifiable objects may find their way into a specimen, particularly those that patients bring from home. Spermatozoa can sometimes be seen. Rarely, pinworm ova may contaminate the urine. In Egypt, ova from bladder infestations with schistosomiasis may be seen.

Summary

To summarize, a properly collected clean-catch, midstream urine after cleansing of the urethral meatus is adequate for complete urinalysis. In fact, these specimens generally suffice even for urine culture. A period of dehydration may precede urine collection if testing of renal concentration is desired, but any specific gravity > 1.022 measured in a randomly collected specimen denotes adequate renal concentration so long as there are no abnormal solutes in the urine.

Another important factor is the interval of time which elapses from collection to examination in the laboratory. Changes which occur with time after collection include: 1) decreased clarity due to crystallization of solutes, 2) rising pH, 3) loss of ketone bodies, 4) loss of bilirubin, 5) dissolution of cells and casts, and 6) overgrowth of contaminating microorganisms. Generally, urinalysis may not reflect the findings of absolutely fresh urine if the sample is > 1 hour old. Therefore, get the urine to the laboratory as quickly as possible**.**

CYTOLOGICAL EXAMINATION

Epithelial cells line the urinary tract and are normally shed into the urine. The urine is examined for the presence of abnormal cells which may indicate cancer of the kidney, ureters, bladder, or urethra. The urine sample is processed in the laboratory and examined under the microscope by a pathologist who looks for the presence of abnormal cells.

First morning urine or 24-hour urine should NOT be used. Since cells in urine have been stored in bladder over several hours, they show degenerative change and are thus not suitable for cytological examination. Fresh voided urine after 3-4 hours should be used, and it should be sent to the laboratory as soon as possible. The sensitivity of urine cytology to detect malignancies is very low (26%), but it shows good specificity of up to 82%. Thus, this test is not good for

screening but very helpful when symptoms are present.

Staining:

- Papanicolau
- Wright‘s
- Immunoperoxidase
- Immunofluorescence

POSSIBLE QUESTIONS

UNIT-I

PART-A (20 MARKS)

(Q.NO 1 TO 20 Online Examination)

PART-B (2 MARKS)

1. Define the term precision.
2. Define the term accuracy.
3. Write a note on Quality Assurance.
4. Define Quality control.
5. Define Trueness.

PART-C (6 MARKS)

1. Explain about the Quality control in clinical biochemistry and its classifications.
2. What are the safety regulations carried out in biochemistry laboratories.
3. Write about the various different methods for collection of blood and how they are preserved.
4. Explain the pre-analytical phase of laboratory diagnostic process.
5. Describe about the analytical phase of laboratory diagnostic process
6. Derive the relationship between precision and Trueness of analytical methods.
7. Write about the post-analytical phase of laboratory diagnostic process.
8. Write about the differences between Quality control and Quality assurance.
9. Explain in detail about the Diagnostic sensitivity and specificity methods for laboratory screening.

KARPAGAM ACADEMY OF HIGHER EDUCATION
DEPARTMENT OF BIOCHEMISTRY
II-M.Sc., BIOCHEMISTRY
CLINICAL BIOCHEMISTRY (18BCP302)
MULTIPLE CHOICE QUESTIONS

Unit - I

S.No	Questions	Option 1	Option 2	Option 3	Option 4	Answer
1	Hypoglycemia is due to	increased insulin	decreased glucagon	inscreased glucagon	decreased glucocorticoids	increased insulin
2	Blood cholesterol level is raised in	hyper thyroidism	hypothyroidism	hypo insulinism	pernicious anemia	hypothyroidism
3	Substance which prevent the accumulation of lipid in the liver is called	Lipophilic factor	Lipophobic factor	Lipotropic factor	Lipidosis	Lipophilic factor
4	Lipoprotein lipase deficiency in blood leads to	Type I primary hyperlipoproteinemia	Type II primary hyperlipoproteinemia	Type III primary hyperlipoproteinemia	Type IV primary hyperlipoproteinemia	Type I primary hyperlipoproteinemia
5	Tangires disease is due to the deficiency of	HDL	Sphingo myclinase	Aryl sulphatase	alphalipoprotein	alphalipoprotein
6	The normal level of total fecal fat excreated is	2-6 g/day	7 - 10 g/day	12-14 g/day	1 - 2 g/day	2-6 g/day
7	The following may lead to fatty liver except one	Alcoholism	Starvation	Carbohydrate rich diet	Uncontrolled diabetes mellitus	Alcoholism
8	The poison causes inhibition of fatty acid oxidation	Hypotaurin	Hypoglycine	Puromycin	Hyposederine	Puromycin
9	Acanthosis -abnormality of	RBC	WBC	Platelets	Phagocytes	RBC
10	The normal level of total cholesterol in blood is	75-300mg/dl	250-400mg/dl	150-250mg/dl	200-350mg/dl	150-250mg/dl
11	The biochemical defect in Type I hyperlipoproteinemia is	Deficiency of LPL	Absence of HDL	Absence of bete lipoprotein	defective LDL receptor	Deficiency of LPL
12	A high blood cholesterol and diminished serum proteins are encountered in	Nephrotic syndrome	Acute nephritis type II	atherosclerosis	Myxedema	atheroselerosis
13	Hypercholesterolemia is due to	Increased synthesis	Increased bile acid formation	Increased dietary fat	Both a and b	Increased synthesis
14	Niemann-pick leads to acumulation of	Ceramide	Cerebroside	Sphingomyelin	Sulpharides	Sphingomyelin
15	The lipoprotein which contains more protein	Chylomicron	VLDL	LDL	HDL	HDL
16	Fatty liver is caused by	CH_3Cl	CCl_4	$MgSO_4$	CH_3COOH	CH_3Cl
17	The normal serum uric acid concentration is in the range of	3 - 7 mg/dl	9 - 10mg/dl	11 - 12 mg/dl	1- 2 mg/dl	3 - 7 mg/dl
18	Hyper uricemia refers to an elevation in the serum _____ concentration	ammonia	urea	uric acid	creatinine	uric acid
19	The excretion of uric acid is otherwise called as	glycosuria	uricosuria	anemia	emotional glycosuria	uricosuria
20	Deposits of uric acid in the joints is called as	uricosuria	goutyarthritis	tophi	arthritis	tophi
21	who was the first to study concentation of urea in blood and its excretion in urine	louis pasteur	ambard	wilson	edward	ambard
22	If the urea volume exceeds 2ml/mt, the rate of urea elimination is at	minimum	normal	maximum	steady	maximum
23	volume of blood cleared of urea per minute can be calculated by the following formula	CX V/A	AXV/B	CXV/B	UxV/B	UxV/B
24	The clearance which occurs when the urinary volume exceeds 2ml/mt is termed as	maximum urea clearance	minimum urea clearance	standard urea clearance	all the above	maximum urea clearance
25	The average normal value for standard urea clearance is	54 ml	64 ml	44 ml	33 ml	54 ml
26	The average normal value for maximum urea clearance is	75 ml	85 ml	65 ml	40 ml	75 ml
27	The urea clearance is proportional to the	surface area of head	surface area of body	surface area of neck	surface area of lungs	surface area of body
28	urea clearance of _____ % indicates normal excretion of kidneys	60	80	70	20	70
29	values of urea clearance between 20 - 40% indicates	mild impairment	severe impairment	moderate impairment	all the above	moderate impairment
30	urea clearance values between_____ indicate mild impairment of excretion of kidneys	40 -70%	20 - 40%	50-60%	20 - 30 %	40 -70%
31	normal values for creatine clearance varies from	95-105 ml/mt	100 - 105 ml/mt	10 -150 ml/mt	5-60 ml/mt	95-105 ml/mt
32	Endogenous creatinine is a _____of body	substrate	product	normal metabolite	all the above	normal metabolite
33	creatinine is neither secreted nor reabsorbed by the tubules. So its clearance gives	Renal function	liver function	glomerular filteration rate	Excretory function of kidney	glomerular filteration rate
34	patients with mild renal disease are recommended to take	high protein diet	moderate protein diet	low protein diet	all the above	low protein diet
35	In terminal uraemia , the urea clearance fallsto about _____ of the normal values	5%	10%	15%	11%	5%
36	Crystals of ammonium magnesium phosphate found in	acid urine	alkaline urine	neutral urine	all the above	alkaline urine
37	phosphate crystals of urine deposits are in _____ form	amorphous	crystalline	colourless	powder	colourless
38	name the type of phosphate crystals which are much commonly seen in urine deposits	coffin lid type	feathery	fernlike	needle shape	coffin lid type
39	calcium hydrogen phosphate most often found crystalline in the form of	rosettes	clusters	rosettes amd star shaped	star shape	rosettes and star shaped
40	Magnesium phosphate is found as _____ in alkaline to weakly acid urines	rhombic plates	diagonal shape	rectangular shape	needle shape	rhombic plates
41	Amorphous phosphates are found in the form of	fine granules	crystals	paste	clusters	fine granules
42	crystals of uric acid are found frequently in the deposits from _____ urines	alkaline	slightly acidic	slightly alkaline	acid urines	acid urines
43	pure uric acid crystals are _____ in nature	colored	colourless	red color	brown color	colourless
44	The pigment found in urine deposit containing uric acid crystals is due to the	inclusion of urinary pigments in the crystal	bile pigments	skin pigments	all the above	inclusion of urinary pigments in the crystals
	Urinary buffer is	Bicarbonate buffer	Peptide chain	Polypeptide chain	Non-protein compound	Bicarbonate buffer
45						
46	Amniotic fluid contains acetyl cholinesterase enzyme. What is the diagnosis ?	Open spina bifida	Gastrochisis	Omphalocele	Osteogenesis imperfecta	Open spina bifida
47	The nervous system performs three important functions. Which of the following is NOT one of those functi	sensory	circulation	integrative	motor	circulation
48	Cerebrospinal fluid (CSF) is	found only in the brain.	a neurotransmitter.	nutritional and cushioning.	contained within the dendrites.	nutritional and cushioning.
49	Meningitis is an infection and inflammation of	the grey matter of the brain and associated	the membranes around the brain.	spinal nerves.	cranial nerves	the membranes around the brain.
50	Why are transfusions given?	To increase the amount of blood	To increase the blood's ability to carry oxyg	To decrease the risk of bleeding	All of the above	All of the above
51	Which parts of the blood can be transfused?	Whole blood	Platelets	Red blood cells	All of the above	All of the above
52	What is the minimum you should weigh to donate blood?	100 pounds	110 pounds	115 pounds	125 pounds	110 pounds
53	How often can a donor give blood?	At any time	Every 2 months	Every 3 months	Every 6 months	Every 2 months
54	How much blood usually is donated at a time?	1 pint	2 pints	1 quart	2 quarts	1 pint
55	Donated blood undergoes screening for which diseases?	AIDS	Viral hepatitis	Diabetes	AIDS and Hepatitis	AIDS and Hepatitis
56	Which agency regulates blood donation?	American Medical Association	U.S. Health and Human Services	FDA	American Red Cross	FDA
57	An advisory panel of experts has suggested that anyone who received transfusions before March 1992 be sc	AIDS	Hepatitis C	Mononucleosis	Leukemia	Hepatitis C
58	Which is the most common blood type among Americans?	O positive	O negative	AB positive	AB negative	O positive
59	Which of the following is the most common type of urine sample and can be taken at any time of the day?	timed urine specimen	random urine specimen	first morning urine specimen	clean-catch midstream urine specimen	random urine specimen
60	Residual urine is	the leakage of urine despite voluntary cont	urine that is collected over a 24-hour period	the measurement of urine remaining in the bladd	urine that is normally voided.	the measurement of urine remaining in the bladder after voiding.
61	Urine leaves the body through the	urinary bladder.	ureters.	urethra.	renal pelvis.	urethra.

UNIT-II

SYLLABUS

Serology and Hematology: C- reactive protein test, immunological test for pregnancy. Rheumatoid arthritis (RA) test, ESR. Coagulation test, prothrombin test. Haemoglobin Normal and abnormal Hb, separation of haemoglobin, Thalassemia, Hemoglobinopathies. Disorder of erythrocyte metabolic pathways, erythrocyte enzyme disorders. Porphyrins and disorder: porphyrias.

C-Reactive Protein (CRP), also known as Pentraxin 1, is a non-glycosylated protein in the Pentraxin family that also includes Pentraxin 2/SAP and Pentraxin 3/TSG-14. CRP is an acute phase reactant, a protein made by the liver and released into the blood within a few hours after tissue injury, the start of an infection, or other cause of inflammation.

A high level of CRP in the blood is a sign that there may be an inflammatory process occurring in the body. Inflammation itself isn't typically a problem, but it can indicate a host of other health concerns, including infection, arthritis, kidney failure, and pancreatitis. High CRP levels may put patients at increased risk for coronary artery disease, which can cause a heart attack. A CRP test is a blood test designed to measure the amount of CRP in the blood.

Principle of CRP Test

The C-Reactive Protein test is based on the principle of the latex agglutination. When latex particles complexed human anti-CRP are mixed with a patient's serum containing C reactive proteins, an visible agglutination reaction will take place within 2 minutes.

Uses of CRP Test

CRP may be used to detect or monitor significant inflammation in an individual who is suspected

of having an acute condition, such as serious bacterial infection like sepsis, a fungal infection and Pelvic inflammatory disease (PID).

The CRP test is useful in monitoring people with chronic inflammatory conditions to detect flare-ups and/or to determine if treatment is effective. Some examples include Inflammatory bowel disease, some forms of arthritis and Autoimmune diseases, such as lupus or vasculitis.

The determination of the CRP-level is useful to monitor the therapy. It is done to check for infection after surgery. CRP levels normally rise within 2 to 6 hours of surgery and then go down by the third day after surgery. If CRP levels stay elevated 3 days after surgery, an infection may be present.

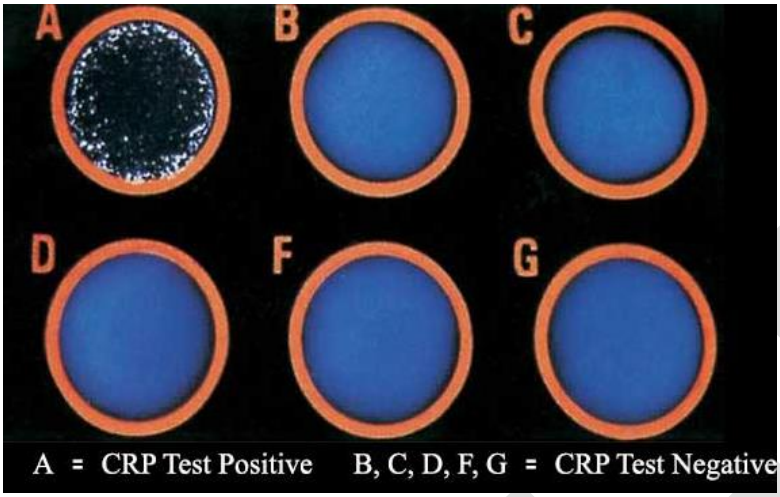
Procedure of CRP Test

Qualitative Test

Bring all reagents and serum sample to Room Temperature and mix latex reagent gently prior to use. Do not dilute the controls and serum.

- Place 1 drop of Serum, Positive control and Negative control on separate reaction circle on glass slide.
- Then add 1 drop of CRP latex reagent to each of the circles.
- Mix with separate mixing sticks and spread the fluid over the entire area of the cell.
- Tilt the slide back and forth slowly for 2 minutes observing preferably under artificial light.

- Observe for visible agglutination.



Immunological test for Pregnancy

1. Pregnancy tests are based on the detection of the human chorionic gonadotropin (hCG). •Human chorionic gonadotropin (hCG) is produced by the placenta shortly after fertilization and reaches detectable levels in urine and serum about 1 week after implantation attachment of the early embryo to the uterine lining. •Levels of hCG continue to rise during the first trimester of pregnancy, making it an excellent marker for pregnancy.

2. Specimens : •Pregnancy tests can be done by either in urine or in blood samples. •Both tests detect the presence of a hormone called human chorionic gonadotropin (hCG).

3. Urine Tests : •Urine specimen must be collected without preservatives in a clean dry container. First morning urine usually contains the highest concentration of hCG, however, urine collected at any time during the day may be used. •If the sample put the collection container into

the refrigerator (fridge), the sample will be rejected. fridge urine leads to less accurate results because stone forming salts become crystallized (from the cold) and thus the results are less viable.

4. Blood Tests: •A quantitative blood test measures the exact amount of Beta hCG in the blood by ElectroChemiLuminescence (ECL)-based immunoassays. • And a qualitative hCG blood test gives a simple positive or negative result to whether pregnant or not (By stripes & cassettes).

5. Laboratory diagnosis of Pregnancy test: No. Methods Time Consuming Serology level 1 Pregnancy Test Reagent by inhibition agglutination (old method). 2 min 2 Pregnancy Test Strip or Cassette by Immunochromatography assay. 10 min 3 Pregnancy Test by Digital Midstream Device. 3 min 4 beta-hCG Test by Electro chemi-luminescence (ECL) technology . 40 min 5 beta-hCG Test by ELISA (enzyme-linked immunosorbent assay). 45 minutes – 2 hours

6. 1-Pregnancy Test by Strips or Cassette • It is a rapid chromatographic immunoassay for the qualitative detection of human chorionic gonadotropin in urine or serum to aid in the early detection of pregnancy. • These pregnancy tests are specifically designed for professional users (doctors, clinics, family planning centers) for determination of early pregnancy, but have also found a place in home pregnancy testing applications due to ease of use and low cost. • The specificity is 98% meaning that test is highly selective for hCG glycoprotein.

7. Principle: •The test uses two lines to indicate results; this test is conductive by immersing the test strip in a urine or serum specimen and observing the formation of colored lines. •The specimen migrates via capillary action along the membrane to react with the colored conjugate.

•Positive specimens reacts with the specific antibody –hCG colored conjugate to form a colored line at the test line region of the membrane. Absence of this colored line suggests a negative result

8. Procedure: 1- Bring the pouch of container to room temperature before opening it. Remove the test strip from the sealed pouch or closed container and use it as soon as possible. 2- With arrows pointing toward the urine or serum specimen. Immerse the test strip vertically in the urine or serum specimen. Do not pass the maximum line on the test strip. 3- Place the test strip on a non-absorbent flat surface, start the timer and wait for the colored line (s) to appear. 4-Read the result after 3 minutes when testing a urine specimen and 5 minutes when testing a serum specimen.

Rheumatoid Arthritis Test:

Aim: To detect the presence of Rheumatoid Factors (RF) which are produced during Rheumatoid arthritis(RA).

Introduction: Rheumatoid arthritis or RA is a chronic and inflammatory disease of flexible (synovial) joints. During this disorder the synovial lymphocytes produce abnormal IgG and in response to this the host immune system generates IgM and these are called Rheumatoid factors (RF). These are autoantibody as they are generated against one's own tissue and for this reason RA is considered as a systematic autoimmune disease. Through a blood test the presence of RF can be detected and consequently RA is diagnosed.

Principle: Agglutination is a reaction of clumping together of antigen-bearing cells, microorganisms or particles in the presence of specific antibodies (agglutinins) in a

suspension. Reaction time for agglutination to occur is shorter compared to other antigen-antibody interactions. Latex agglutination makes use of latex particles which are built from different organic materials to a desired diameter, and may be functionalized with chemical groups to facilitate attachment of molecules. Latex agglutination tests have been in use since 1956 to detect a wide range of analytes in the clinical laboratory. The first description of a test based on latex agglutination was the 'Rheumatoid Factor Test' proposed by Singer and Plotz in 1956. In this method the patient's blood sample is mixed with tiny latex beads covered with human antibodies (IgG). The latex beads clump or agglutinate if rheumatoid factor (IgM RF) is present.

Procedure:

1. Before starting the experiment, bring all reagents to room temperature and mix well.
2. Take 10µl of test serum sample on one of the latex disposable slide circle (As shown in fig.1).
3. Take 10 µl of Positive and Negative control each on other circles.
4. Add 25 µl of Latex reagent to al these three circles. Do not let the dropper tip touch the liquid on the slide.
5. Using disposable mixing sticks mix all the contents uniformly over the entire circles of slide.
6. Rock the slide gently, back and forth for 2 minutes. Observe for agglutination.

Observation and Result:

After mixing the Latex reagent with Positive control, Negative control and Test sample separately observe for the agglutination reaction.

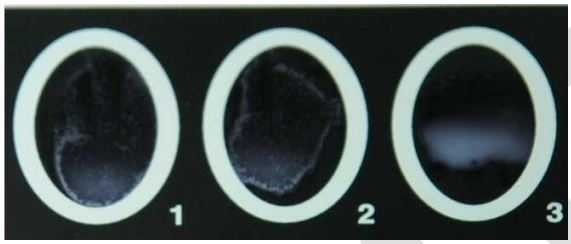


Fig: Agglutination reaction for Latex reagent with Positive, Negative control and Test sample

Circle 1: Positive Control Circle 2: Test sample Circle 3: Negative Control

Interpretation:

Agglutination of latex particles is considered a positive reaction, indicating the presence of rheumatoid factor at a significant and detectable level.

Prothrombin Time

A prothrombin time test measures how quickly the blood clots. Sometimes called a PT or pro time test, a prothrombin time test uses a sample of the blood. Prothrombin is a protein produced by your liver. It is one of many factors in the blood that help it to clot appropriately.

It is done to

- Monitor the effectiveness of a blood-thinning medication of an individual
- Diagnose liver problems
- Assess the blood's ability to clot before the surgery

Prothrombin time (PT) is measured in seconds. Most of the time, results are given as what is called INR (international normalized ratio). If you are not taking blood thinning medicines, such as warfarin, the normal range for your PT results is: 11 to 13.5 seconds.

A phlebotomist (a person specially trained in drawing blood) draw a small needle to draw blood from a vein, usually in the arm or hand. A laboratory specialist will add chemicals to the blood to see how long it takes for a clot to form.

Hemoglobin Variants

Hemoglobin S: this is the primary hemoglobin in people with sickle cell disease (also known as sickle cell anemia). Approximately 1 in 375 African American babies are born with sickle cell disease, and about 100,000 Americans live with the disorder, according to the Centers for Disease Control and Prevention. Those with Hb S disease have two abnormal beta chains and two normal alpha chains. The presence of hemoglobin S causes the red blood cell to deform and assume a sickle shape when exposed to decreased amounts of oxygen (such as might happen when someone exercises or has infection in the lungs). Sickled red blood cells are rigid and can block small blood vessels, causing pain, impaired circulation, and decreased oxygen delivery, as well as shortened red cell survival. A single beta (βS) copy (known as sickle cell trait, which is present in approximately 8% of African Americans) typically does not cause significant

symptoms unless it is combined with another hemoglobin mutation, such as that causing Hb C or beta thalassemia.

Hemoglobin C: about 2-3% of African Americans in the United States are heterozygotes for hemoglobin C (have one copy, known as hemoglobin C trait) and are often asymptomatic. Hemoglobin C disease (seen in homozygotes, those with two copies) is rare (0.02% of African Americans) and relatively mild. It usually causes a minor amount of hemolytic anemia and a mild to moderate enlargement of the spleen.

Hemoglobin E: Hemoglobin E is one of the most common beta chain hemoglobin variants in the world. It is very prevalent in Southeast Asia, especially in Cambodia, Laos, and Thailand, and in individuals of Southeast Asian descent. People who are homozygous for Hb E (have two copies of βE) generally have a mild hemolytic anemia, microcytic red blood cells, and a mild enlargement of the spleen. A single copy of the hemoglobin E gene does not cause symptoms unless it is combined with another mutation, such as the one for beta thalassemia trait.

Hemoglobin F: Hb F is the primary hemoglobin produced by the fetus, and its role is to transport oxygen efficiently in a low oxygen environment. Production of Hb F decreases sharply after birth and reaches adult levels by 1-2 years of age. Hb F may be elevated in several congenital disorders. Levels can be normal to significantly increased in beta thalassemia and are frequently increased in individuals with sickle cell anemia and in sickle cell-beta thalassemia. Individuals with sickle cell disease and increased Hb F often have a milder disease, as the F hemoglobin inhibits sickling of the red cells. Hb F levels are also increased in a rare condition called hereditary persistence of fetal hemoglobin (HPFH). This is a group of inherited disorders

in which Hb F levels are increased without the signs or clinical features of thalassemia. Different ethnic groups have different mutations causing HPFH. Hb F can also be increased in some acquired conditions involving impaired red blood cell production. Some leukemias and other myeloproliferative neoplasms are also associated with mild elevation in Hb F.

Hemoglobin H: Hb H is an abnormal hemoglobin that occurs in some cases of alpha thalassemia. It is composed of four beta (β) globin chains and is produced due to a severe shortage of alpha (α) chains. Although each of the beta (β) globin chains is normal, the tetramer of 4 beta chains does not function normally. It has an increased affinity for oxygen, holding onto it instead of releasing it to the tissues and cells. Hemoglobin H is also associated with significant breakdown of red blood cells (hemolysis) as it is unstable and tends to form solid structures within red blood cells. Serious medical problems are not common in people with hemoglobin H disease, though they often have anemia.

Hemoglobin Barts: Hb Barts develops in fetuses with alpha thalassemia. It is formed of four gamma (γ) protein chains when there is a shortage of alpha chains, in a manner similar to the formation of Hemoglobin H. If a small amount of Hb Barts is detected, it usually disappears shortly after birth due to dwindling gamma chain production. These children have one or two alpha gene deletions and are silent carriers or have the alpha thalassemia trait. If a child has a large amount of Hb Barts, he or she usually has hemoglobin H disease and a three-gene deletion. Fetuses with four-gene deletions have hydrops fetalis and usually do not survive without blood transfusions and bone marrow transplants.

Testing for hemoglobin abnormalities (variants) is done:

To screen for common and clinically significant hemoglobin variants in newborns. In all states, this has become a standard part of newborn screening. Infants with variants such as Hb S can benefit from early detection and treatment.

As part of prenatal screening, on high-risk women including those with an ethnic background associated with a higher prevalence of hemoglobin variants (such as those of African descent) and those with affected family members. Screening may also be done in conjunction with genetic counseling prior to pregnancy to determine possible carrier status of potential parents.

To identify variants in asymptomatic parents with an affected child. To identify hemoglobin variants in those with symptoms of unexplained anemia, with red blood cells (RBCs) that are small and/or paler than normal (microcytosis and hypochromia). It may also be ordered as part of an anemia investigation, or when someone has signs and symptoms associated with hemoglobin variants.

Laboratory tests

Laboratory testing for hemoglobin variants is an exploration of the "normalness" of an individual's red blood cells, an evaluation of the hemoglobin inside the RBCs, and/or an analysis of relevant gene mutations. Each test provides a piece of the puzzle, giving the clinician important information about the hemoglobins that may be present. Testing typically includes:

CBC (complete blood count): The CBC is a snapshot of the cells circulating in the blood. Among other things, the CBC will tell the doctor how many red blood cells are present, how much hemoglobin is in them, and give the doctor an evaluation of the average size of the red

blood cells present. Mean corpuscular volume (MCV) is a measurement of the size of the red blood cells. A low MCV is often the first indication of thalassemia. If the MCV is low and iron-deficiency has been ruled out, the person may be a carrier of the thalassemia trait or have a hemoglobin variant that results in smaller than normal RBCs (for example, Hb E).

Blood smear (also called a peripheral smear): In this test, a trained laboratorian looks under the microscope at a thin layer of blood on a slide treated with a special stain. The number and type of white blood cells, red blood cells, and platelets can be evaluated to see if they are normal and mature. With a hemoglobinopathy, the red blood cells may be:

Smaller than normal (microcytic)

Paler than normal (hypochromic)

Varying in size (anisocytosis) and shape (poikilocytosis, e.g., sickle-shaped cells)

Having a nucleus (nucleated red blood cell, not normal in a mature RBC) or crystal (e.g., C crystal)

Having uneven hemoglobin distribution (producing "target cells" that look like a bull's-eye under the microscope).

The greater the percentage of abnormal-looking red blood cells, the greater the likelihood of an underlying disorder.

Hemoglobinopathy evaluation: These tests identify the type, and measure the relative amount, of the different types of hemoglobin present in an individual's red blood cells. Most of the common variants can be identified using one of these tests or a combination. The relative amounts of any variant hemoglobin detected can help diagnose combinations of hemoglobin

variants and thalassemia (compound heterozygotes).

Genetic testing: These tests are used to investigate deletions and mutations in the alpha and beta globin-producing genes. Family studies can be done to evaluate carrier status and the types of mutations present in other family members. Genetic testing is not routinely done but can be used to help confirm hemoglobin variants, thalassemia, and to determine carrier status.

Porphyria (por-FEAR-e-uh) refers to a group of disorders that result from a buildup of natural chemicals that produce porphyrin in your body. Porphyrins are essential for the function of hemoglobin — a protein in your red blood cells that links to porphyrin, binds iron, and carries oxygen to your organs and tissues. High levels of porphyrins can cause significant problems. There are two general categories of porphyria: acute, which mainly affects the nervous system, and cutaneous, which mainly affects the skin. Some types of porphyria have both nervous system symptoms and skin symptoms.

Signs and symptoms of porphyria vary, depending on the specific type and severity. Porphyria is usually inherited — one or both parents pass along an abnormal gene to their child.Although porphyria can't be cured, certain lifestyle changes to avoid triggering symptoms may help you manage it. Treatment for symptoms depends on the type of porphyria you have.

Symptoms

Symptoms of porphyria can vary widely in severity, by type and among individuals. Some people with the gene mutations that cause porphyria never have any symptoms.

Acute porphyrias

Acute porphyrias include forms of the disease that typically cause nervous system symptoms, which appear quickly and can be severe. Symptoms may last days to weeks and usually improve slowly after the attack. Acute intermittent porphyria is the common form of acute porphyria.

Signs and symptoms of acute porphyria may include:

- Severe abdominal pain
- Pain in your chest, legs or back
- Constipation or diarrhea
- Nausea and vomiting
- Muscle pain, tingling, numbness, weakness or paralysis
- Red or brown urine
- Mental changes, such as anxiety, confusion, hallucinations, disorientation or paranoia
- Breathing problems
- Urination problems
- Rapid or irregular heartbeats you can feel (palpitations)
- High blood pressure
- Seizures
- Cutaneous porphyrias

- Cutaneous porphyrias include forms of the disease that cause skin symptoms as a result of sensitivity to sunlight, but these forms don't usually affect your nervous system. Porphyria cutanea tarda (PCT) is the most common type of all the porphyrias.

As a result of sun exposure, the patient may experience:

1. Sensitivity to the sun and sometimes artificial light, causing burning pain
2. Sudden painful skin redness (erythema) and swelling (edema
3. Blisters on exposed skin, usually the hands, arms and face
4. Fragile thin skin with changes in skin color (pigment)
5. Itching
6. Excessive hair growth in affected areas
7. Red or brown urine

KARPAGAM ACADEMY OF HIGHER EDUCATION
DEPARTMENT OF BIOCHEMISTRY
II-M.Sc., BIOCHEMISTRY
CLINICAL BIOCHEMISTRY (18BCP302)
MULTIPLE CHOICE QUESTIONS

unit II

S.NO.	QUESTION	OPTION A	OPTION B	OPTION C	OPTION D	ANSWER
1	The regulatory enzyme for haem synthesis is	ALA synthetase	Haem synthetase	Myoglobin lyase	Carboxypeptidase	ALA synthetase
2	Two alpha and two beta chains are present in	Embryonic Hb	Foetal Hb	HbA	HbS	HbA
3	Regulation of haem synthesis occurs by	Covalent modification of iron	Repression of ALA	Induction	Allosteric regulation of ALA	Repression of ALA
4	Gamma polypeptide chains are present only in	Foetal Hb	HbA	Embryonic Hb	HbS	Foetal Hb
5	2, 3 – biphospho glycerate is attached to the following form of hemoglobin	T. Form	R.Form	Both of the above	Neither of the above	T.Form
6	2, 3, - Biphosphoglycerate is released from hemoglobulin when	Oxygen tension decreases	Oxygen tension increases	Glycolysis increases	Glycolysis decreases	Oxygen tension increases
7	Sigmoidal oxygen dissociation curve is a property of	Hemoglobin	Carboxy hemoglobin	Myoglobin	Methemaglobin	Hemoglobin
8	Cyanmethaemoglobin can be formed	Oxy Hb	Met Hb	Carboxy Hb	All of the above	Met Hb
9	HbS is formed by substitution of an amino acid at position 6 in	Alpha chain	Beta chain	Gamma chain	Any chain	Beta chain
10	Haemoglobin contains the number of gram atoms of iron per mole ferrous state	1	2	3	4	4
11	The molecular weight of hemoglobin	44,550	54,450	64,450	74,450	64,450
12	The globulin of the hemoglobin is a protein composed of	6 parallel layers	4 parallel layers	3 parallel layers	2 parallel layers	4 parallel layers
13	Haem is synthesized by the incorporation of ferrous ion (Fe^{++}) into protoporphyrin III by	Ferroxidase	Ferroreductase	Ferrochelatese	None of the above	Ferrochelatese
14	The total number of amino acid in globulin	544	554	564	574	574
15	Haemoglobin takes up the number of molecules of oxygen	1	2	4	6	4
16	Carboxyhemoglobin is formed by		CO_2	HCO_3	CO_3	CO
17	One mol. of hemoglobin contains histidine	5	15	25	35	35
18	The color of cyanomethemoglobin	Yellow	Pink	Brown	Bright Red	Bright Red
19	Methemoglobin can be reduced to hemoglobin by	Removal of hydrogen	Vitamin C	Glutathione	Creatinine	Vitamin C
20	The iron of heme is coordinated in β – chains at positions	43 and 72	53 and 82	63 and 92	73 and 102	63 and 92
21	In thalassemia an amino acid is substituted in	Alpha chain	Beta chain	Alpha and Beta chain	There is no substitution	There is no substitution
22	C-Reactive Protein contains------- Mol.wt	115,000- 140, 00	140,000- 175,000	85,000-115,000	175,000- 200,000	115,000- 140, 00
23	CRP normally present in plasma----µg/dl	. >800 µg/dl	<800 µg/dl	<500-µg/dl	>500 µg/dl	<800 µg/dl
24	. CGα contains	94aa	93aa	92aa	95aa	92aa
25	HbC is formed by substitution of an amino acid at position 6 in β-chain	. Lys- Glu	Glu-Lys	. Glu-Val	Glu-Gln	Glu-Lys
26	Which particle is used for the Anti –hcG serum slide test?	hcG coated particles	Latex coated particles	Anti latex coated particles	None of the above	Latex coated particles
27	C-reactive protein is a ____	β-Globulin	α -globulin	γ -Globulin	None of the above	β-Globulin
28	The concentration of the C- reactive protein present in the adult male is	Less than 1mg/100ml	more than 1mg/100ml	Less than 0.5mg/100ml	Less than 1mg/50ml	Less than 1mg/100ml
29	C-reactive protein precipitates with the____ polysaccharide	a group	b group	d group	c group	c group
30	C-reactive protein precipitates with the c group polysaccharide of____	Streptococci	bacillus	Pneumococci	staphylococci	Pneumococci
31	C-reactive protein remains increased in presence of solid tumor is called	Leukemia	. Hodgkin's disease	Bence-jones disease	Both A and B	Both A and B
32	Prothrombin is formed in the presence of	Vit A	Vit B	Vit K	Vit H	Vit K
33	Normal value for the prothrombin time is	10-16 sec	10-16 min	Less than 10 sec	more than 10 min	10-16 Sec
34	PT is used mostly in controlling___ therapy	Heart disease	renal disorder	Anti-coagulant therapy	urinary track infections	Anti-coagulant therapy
35	The Normal value for prothrombin index is	50-60%	70-100%	110-120%	10-50%	70-100%
36	Hepatic Porphyria is divided into ___ groups	4	2	3	6	3
37	Intermittent acute Porphyria is also called as	Peroxysomal Porphyria	Paroxysmal Porphyria	Lysosomal Porphyria	Lyposomal Porphyria	Paroxysmal Porphyria
38	Mixed or combined Hepatic Porphyria is called as	Paroxysmal Porphyria	Lyposomal Porphyria	Variegate Porphyria	Peroxysomal Porphyria	Variegate Porphyria
39	In the biosynthesis of porphyrins, which of the coenzyme is required for δ-ALA formation	FAD	FMN	B_6 –PO_4	NAD^+	B_6 –PO_4
40	Which of the porphyrin go into the formation of protoporphyrin IX?	. Type I series	type I series type II series	Type III series	None of the above	Type III series
41	In mammalian liver, conversion of coproporhyrinogen III to protoporphyrinogen IX requires tl	ATP	Molecular oxygen	Mg^{2+}	B_6 –PO_4	Molecular oxygen
42	Uroporphyrin and coprporphyrin of which series is excreted in urine in congenital erythropoeit	type I series	type II series	type III series	type IV series	type I series
43	The enzyme which catalyses the synthesis of Heme from protoporphyrinIX is	Ferro reductase	Ferrocatalase	Ferro oxidase	All the above	Ferrocatalase
44	Methaemoglobin contains	A denatured globin	A Ferroprotoporphyrin	A ferri protoporphyrin	None of the above	A ferri protoporphyrin
45	.Thalassaemias associated with severe anemia of infancy is called as	Peroxysomal anemia	Paroxysmal anemia	Lysosomal anemia	Cooley's anemia	Cooley's anemia
46	The Rapoport-Luebering cycle is involved in the ____ pathway	Glycogenesis	Kreb's Cycle	Erythrocyte metabolism	Protein metabolism	Erythrocyte metabolism
47	The Rapoport-Luebering cycle regulates the relative amounts of _____	FAD	NADH	NADPH	UTP	NADH
48	The most useful marker for the pregnancy is____	Placental hormone	chorionic gonodotrophion	acental and chorionic gonadotrop	glucagan	cental and chorionic gonadotropin
49	When a blastocyst implants in a location other than the body of the uterus, the condition is call	Ectopic pregnancy	Endopic pregnancy	Icteric index	Idiopathic	Ectopic pregnancy
50	Qualitative tests for CG in _____ used primarily	Urine	Blood	Blood and Urine	Saliva	Blood and Urine
51	To diagnose the pregnancy _____ is used	Blood CG	Urine CG	Blood and Urine	Saliva	Urine CG
52	Hemoglobin –S forms long, ropelike polymers when deoxygenated that aggregates of such po	Tactoid	Octoide	Peptide	terroid	Tactoid
53	To detect the Hemoglobin ____ is used	Electrophoresis	Chromatography	physical methods	TLC	Electrophoresis
54	To detect the Hemoglobin ____ is used	Immunoassay	Molecular Technique	ımunoassay &Molecular Technic	None of the above	nunoassay &Molecular Technique
55	Rheumatoid arthritis is determined by which particles	Gold	Silver	Latex	Platinum	Latex
56	Porphyrin disorder is classified in to ___ types	2	3	4	5	2
57	In Congenital Erythropoietic porphyria the Urine color is	Port wine	Yellow	Green	Black	Port Wine
58	enzyme deficiency in Intermittent acute porphyria is	Uroporphyrinogen I synthetas	Uroporphyrinogen II synthetase	Uroporphyrinogen IX synthetase	Uroporphyrinogen V synthetase	Uroporphyrinogen I synthetase
59	Person suffering from inflammatory diseases will have alterations in	C-reactive protein	digestive enzymes	glucogenic enzymes	steroidogenic proteins	C-reactive protein
60	C-reactive protein is a(n)	monomer	dimer	pentamer	trimer	pentamer

UNIT-III

SYLLABUS

Myocardial infarctions, hepatobiliary disease. - Enzyme tests in determination of myocardial infarction. Diagnostic enzymes: Principles of diagnostic enzymology. Clinical significance of aspartate aminotransferase, alanine aminotransferase, creatine kinase, aldolase and lactate dehydrogenase. Enzymes of pancreatic origin and biliary tract. Clinical significance of electrolytes. AIDS- Clinical diagnosis. Diagnosis of genetic diseases by molecular biology techniques (cystic fibrosis, Hemachromatosis, thalassemias, sickle cell diseases).

Myocardial infarction

Myocardial infarction (MI), commonly known as a heart attack, occurs when blood flow decreases or stops to a part of the heart, causing damage to the heart muscle. The most common symptom is chest pain or discomfort which may travel into the shoulder, arm, back, neck, or jaw. Often it occurs in the center or left side of the chest and lasts for more than a few minutes.The discomfort may occasionally feel like heartburn. Other symptoms may include shortness of breath, nausea, feeling faint, a cold sweat, or feeling tired. About 30% of people have atypical symptoms.Women more often have atypical symptoms than men.[Among those over 75 years old, about 5% have had an MI with little or no history of symptoms. An MI may cause heart failure, an irregular heartbeat, cardiogenic shock, or cardiac arrest

Myocardial infarction (MI), colloquially known as "heart attack," is caused by decreased or complete cessation of blood flow to a portion of the myocardium. Myocardial infarction may be "silent" and go undetected, or it could be a catastrophic event leading to hemodynamic deterioration and sudden death. Most myocardial infarctions are due to underlying coronary artery disease, the leading cause of death in the United States. With coronary artery occlusion, the myocardium is deprived of oxygen. Prolonged deprivation of oxygen supply to the myocardium can lead to myocardial cell death and necrosis. Patients can present with chest discomfort or pressure that can radiate to the neck, jaw, shoulder, or arm. In addition to the history and physical exam, myocardial ischemia may be associated with ECG changes and elevated biochemical markers such as cardiac troponins.

As stated above, myocardial infarction is closely associated with coronary artery disease. INTERHEART is an international multi-center case-control study which delineated the following modifiable risk factors for coronary artery disease:

1. Smoking
2. Abnormal lipid profile/blood apolipoprotein (raised ApoB/ApoA1)
3. Hypertension
4. Diabetes mellitus
5. Abdominal obesity (waist/hip ratio) (greater than 0.90 for males and greater than 0.85 for females)
6. Psychosocial factors such as depression, loss of the locus of control, global stress, financial stress, and life events including marital separation, job loss, and family conflicts

7. Lack of daily consumption of fruits or vegetables

8. Lack of physical activity

9. Alcohol consumption (weaker association, protective)

The INTERHEART study showed that all the above risk factors were significantly associated with acute myocardial infarction except for alcohol consumption which showed a weaker association. Smoking and abnormal apolipoprotein ratio showed the strongest association with acute myocardial infarction. The increased risk associated with diabetes and hypertension were found to be higher in women, and the protective effect of exercise and alcohol were also found to be higher in women. Other risk factors include a moderately high level of plasma homocysteine, which is an independent risk factor of MI.

Elevated plasma homocysteine is potentially modifiable and can be treated with folic acid, vitamin B6, and vitamin B12. Some non-modifiable risk factors for myocardial infarction include advanced age, male gender (males tend to have myocardial infarction earlier in life), genetics (there is an increased risk of MI if a first-degree relative has a history of cardiovascular events before the age of 50). The role of genetic loci that increase the risk for in MI is under active investigation.

Epidemiology

The most common cause of death and disability in the western world and worldwide is coronary artery disease. Based on 2015 mortality data from the National Health Interview Survey (NHIS-CDC), MI mortality was 114,023, and MI any-mention mortality (i.e., MI is mentioned as a contributing factor in the death certificate) was 151,863. As per the National Health and

Nutrition Examination Survey (NHANES)-CDC data from 2011 to 2014 an estimated 16.5 million Americans older than 20 years of age have coronary artery disease, and the prevalence was higher in males than females for all ages. As per the NHANES 2011 through 2014, the overall prevalence of MI is 3.0% in US adults older than 20 years of age.

Prevalence of MI in the US Sub-Populations

Non-Hispanic Whites

4.0% (Male)

2.4% (Female)

Non-Hispanic Blacks

3.3% (Male)

2.2% (Female)

Hispanics

2.9% (Male)

2.1% (Female)

Non-Hispanic Asians

2.6% (Male)

0.7% (Female)

Based on the Atherosclerosis Risk in Communities Study (ARIC) performed by National Heart, Lung and Blood Institute (NHLBI) collected between 2005 and 2014, the estimated annual incidence is 605,000 new MIs and 200,000 recurrent MIs.

The ARIC study also found that the average age at first MI is 65.6 years for males and 72.0 years for females. In the past decades, several studies have shown a declining incidence of MI in the United States.

Pathophysiology

The acute occlusion of one or multiple large epicardial coronary arteries for more than 20 to 40 minutes can lead to acute myocardial infarction. The occlusion is usually thrombotic and due to rupture of a plaque formed in the coronary arteries. The occlusion leads to a lack of oxygen in the myocardium which results in sarcolemmal disruption and myofibril relaxation.These changes are one of the first ultrastructural changes in the process of MI which are followed by mitochondrial alterations. The prolonged ischemia ultimately results in liquefactive necrosis of myocardial tissue. The necrosis spreads from sub-endocardium to sub-epicardium. Sub-epicardium is believed to have increased collateral circulation which delays its death. Depending on the territory affected by the infarction, the cardiac function is compromised. Due to negligible regeneration capacity of the myocardium, the infarcted area heals by scar formation, and often, the heart is remodeled characterized by dilation, segmental hypertrophy of remaining viable tissue and cardiac dysfunction.

History and Physical

The imbalance between oxygen supply and the demand leads to myocardial ischemia and can sometimes lead to myocardial infarction. The patient's history, electrocardiographic findings, and elevated serum biomarkers are helpful in identifying ischemic symptoms. Myocardial

ischemia can present as chest pain, upper extremity pain, mandibular or epigastric discomfort that occurs during exertion or at rest. Myocardial ischemia can also present as dyspnea or fatigue which are known to be ischemic equivalents.[14] The chest pain is usually retrosternal and is sometimes described as the sensation of pressure or heaviness. The pain often radiates to the left shoulder, neck or arms with no obvious precipitating factors and it may be intermittent or persistent. The pain usually lasts for more than 20 minutes. It is usually not affected by positional changes or active movement of the region. Additional symptoms such as sweating, nausea, abdominal pain, dyspnea, and syncope may also be present. The MI can also present atypically with subtle findings such as palpitations, or more dramatic manifestations, such as cardiac arrest. The MI can sometimes present with no symptoms.

Evaluation

The three components in the evaluation of the MI are clinical features, ECG findings, and cardiac biomarkers.

ECG

The resting 12 lead ECG is the first-line diagnostic tool for the diagnosis of an acute coronary syndrome (ACS). It should be obtained within 10 minutes of the patient's arrival in the emergency room. Acute MI is often associated with dynamic changes in the ECG waveform. Serial ECG monitoring can provide important clues to the diagnosis if the initial EKG is non-diagnostic at initial presentation. Serial or continuous ECG recordings may be helpful in determining reperfusion or re-occlusion status. A large and prompt reduction in ST-segment elevation is usually seen in reperfusion.

ECG findings suggestive of ongoing coronary artery occlusion (in the absence of left ventricular hypertrophy and bundle branch block):

ST-segment elevation in two contiguous lead (measured at J-point) of

Greater than 5 mm in men younger than 40 years, greater than 2 mm in men older than 40 years, or greater than 1.5 mm in women in leads V2-V3 and/or 1. Greater than 1 mm 2. in all other leads *ST-segment depression and T-wave changes* New horizontal or down-sloping ST-segment depression greater than 5 mm in 2 contiguous leads and/or T inversion greater than 1 mm in two contiguous leads with prominent R waves or R/S ratio of greater than 1

The hyperacute T-wave amplitude, with prominent symmetrical T waves in two contiguous leads, may be an early sign of acute MI that may precede the ST-segment elevation. Other ECG findings associated with myocardial ischemia include cardiac arrhythmias, intraventricular blocks, atrioventricular conduction delays, and loss of precordial R-wave amplitude (less specific finding). ECG findings alone are not sufficient to diagnose acute myocardial ischemia or acute MI as other conditions such as acute pericarditis, left ventricular hypertrophy (LVH), left bundle branch block (LBBB), Brugada syndrome, Takatsubo syndrome (TTS), and early repolarization patterns also present with ST deviation. ECG changes associated with prior MI (in the absence of left ventricular hypertrophy and left bundle branch block): Any Q wave in lead V2-V3 greater than 0.02 s or QS complex 1. in leads V2-V3 Q wave > 03 s and greater than 1 mm deep or QS complex in leads I, II, aVL, aVF or V4-V6 in any two leads of contiguous lead grouping (I, aVL; V1-V6; II, III, aVF) 2. R wave > 0.04 s in V1-V2 and R/S greater than 1 with a concordant positive T wave in the absence of conduction defect

Biomarker Detection of MI

Cardiac troponins (I and T) are components of the contractile apparatus of myocardial cells and expressed almost exclusively in the heart. Elevated serum levels of cardiac troponin are not specific to the underlying mode of injury (ischemic vs. tension). The rising and/or falling pattern of cardiac troponins (cTn) values with at least one value above the 99 percentile of upper reference limit (URL) associated with symptoms of myocardial ischemia would indicate an acute MI. Serial testing of cTn values at 0 hours, 3 hours, and 6 hours would give a better perspective on the severity and time course of the myocardial injury. Depending on the baseline cTn value the rising/falling pattern is interpreted. If the cTn baseline value is markedly elevated, a minimum change of greater than 20% in follow up testing is significant for myocardial ischemia. Creatine kinase MB isoform can also be used in the diagnosis of MI, but it is less sensitive and specific than cTn level.

Imaging

Different imaging techniques are used to assess myocardial perfusion, myocardial viability, myocardial thickness, thickening and motion, and the effect of myocyte loss on the kinetics of para-magnetic or radio-opaque contrast agents indicating myocardial fibrosis or scars. Some imaging modalities that can be used are echocardiography, radionuclide imaging, and cardiac magnetic resonance imaging (cardiac MRI). Regional wall motion abnormalities induced by ischemia can be detected by echocardiography almost immediately after the onset of ischemia when greater than 20% transmural myocardial thickness is affected. Cardiac MRI provides an accurate assessment of myocardial structure and function.

Treatment / Management

Acute Management

Reperfusion therapy is indicated in all patients with symptoms of ischemia of less than 12-hour duration and persistent ST-segment elevation. Primary percutaneous coronary intervention (PCI) is preferred to fibrinolysis if the procedure can be performed < 120 minutes of ECG diagnosis. If there is no immediate option of PCI (> 120 minutes), fibrinolysis should be started within 10 minutes of STEMI after ruling out contraindications. If transfer to a PCI center is possible in 60 to 90 minutes after a bolus of the fibrinolytic agent and patient meets reperfusion criteria, a routine PCI can be done, or a rescue PCI can be planned.[19][17] If fibrinolysis is planned, it should be carried out with fibrinspecific agents such as tenecteplase, alteplase or reteplase (class I). *Relief of pain, breathlessness, and anxiety:* The chest pain due to myocardial infarction is associated with sympathetic arousal which causes vasoconstriction and increased workload for the ischemic heart. Intravenous opioids (e.g., morphine) are the analgesics most commonly used for pain relief (Class IIa). The results from CRUSADE quality improvement initiative has shown that the use of morphine may be associated with a higher risk of death and adverse clinical outcomes. The study was done from the CIRCUS (Does Cyclosporine Improve outcome in STEMI patients) database which showed no significant adverse events associated with morphine use in a case of anterior STsegment elevation MI. A mild anxiolytic (usually a benzodiazepine) may be considered in very anxious patients (class IIa). Supplemental oxygen is indicated in patients with hypoxemia (SaO2 < 90% or PaO2 < 60mm Hg) (Class I).

Nitrates: Intravenous nitrates are more effective than sublingual nitrates with regard to symptom relief and regression of ST depression (NSTEMI). The dose is titrated upward until symptoms are relieved, blood pressure is normalized in hypertensive patients, or side effects such as a headache and hypotension are noted. *Beta-blockers:* This group of drugs reduces myocardial oxygen consumption by lowering heart rate, blood pressure, and myocardial contractility. They block beta receptors in the body including the heart and reduce the effects of circulating catecholamines. Beta-blockers should not be used in suspected coronary vasospasm or cocaine use. *Platelet inhibition:* Aspirin is recommended in both STEMI and NSTEMI in an oral loading dose of 150 to 300 mg (non-enteric coated formulation) and a maintenance dose of 75 to 100 mg per day long-term regardless of treatment strategy (class I). Aspirin inhibits thromboxane A2 production throughout the lifespan of the platelet. Most P2Y12 inhibitors are inactive prodrugs (except for ticagrelor which is an orally active drug which does not require activation) that require oxidation by hepatic cytochrome P450 system to generate an active metabolite which selectively inhibits P2Y12 receptors irreversibly. Inhibition of P2Y12 receptors leads to inhibition of ATP induced platelet aggregation. The commonly used P2Y12 inhibitors are clopidogrel, prasugrel, and ticagrelor. The loading dose for clopidogrel is 300 to 600 mg loading dose followed by 75 mg per day. Prasugrel, 60 mg loading dose, and 10 mg per day of a maintenance dose have a faster onset when compared to clopidogrel. Patients undergoing PCI should be treated with dual antiplatelet therapy (DAPT) with aspirin + P2Y12 inhibitor and a parenteral anticoagulant. In PCI, use of prasugrel or ticagrelor is found to be superior to clopidogrel. Aspirin and clopidogrel are also found to decrease the number of ischemic events in

NSTEMI and UA. The anticoagulants used during PCI are unfractionated heparin, enoxaparin, and bivalirudin. The bivalirudin is recommended during primary PCI if the patient has heparin-induced thrombocytopenia.

Long-Term Management

Lipid-lowering treatment: It is recommended to start high-intensity statins which reduce low-density lipoproteins (LDLs) and stabilize atherosclerotic plaques. High-density lipoproteins are found to be protective. *Anti-thrombotic therapy:* Aspirin is recommended lifelong, and the addition of another agent depends on the therapeutic procedure done such as PCI with stent placement. ACE inhibitors are recommended in patients with systolic left ventricular dysfunction, or heart failure, hypertension or diabetes. Beta-blockers are recommended in patients with LVEF less than 40% if no other contraindications are present. Anti-hypertensive therapy can maintain a blood pressure goal less than 140/90 mm Hg. Mineralocorticoid receptor antagonist therapy is recommended in a patient with left ventricular dysfunction (LVEF less than 40%). Glucose lowering therapy in diabetics to achieve current blood sugar goals.

Lifestyle Modifications

Smoking cessation is the most cost-effective secondary measure to prevent MI. Smoking has a pro-thrombotic effect which has a strong association with atherosclerosis and myocardial infarction. *Diet, alcohol and weight control:* A diet low in saturated fat with a focus on whole grain products, vegetables, fruits and, the fish is considered cardioprotective. The target level for body weight is body mass index of 20 to 25 kg/m2 and waist circumference of < 94 cm for the men and < 80 cm for the female.

Differential Diagnosis

1. Angina pectoris

2. NSTEMI

3. STEMI

4. Pulmonary Embolism

5. Pneumothorax

Complications

Type and Manifestation

I: Ischemic

Reinfarction

Extension of infarction

Angina

II: Arrhythmias

Supraventricular or ventricular arrhythmia

Sinus bradycardia and atrioventricular block

III: Mechanical

Myocardial dysfunction

Cardiac failure

Cardiogenic shock

Cardiac rupture (Free wall rupture, Ventricular septal rupture, papillary muscle rupture)

IV: Embolic

Left ventricular mural thrombus,

Peripheral embolus

V: Inflammatory

Pericarditis (Infarct associated pericarditis, late pericarditis or post-cardiac injury pericarditis).

Pericardial effusion

Enhancing Healthcare Team Outcomes

The key to management of MI is time until treatment. Thus, healthcare professionals including nurses who work in the emergency department must be familiar with the symptoms of MI and the importance of rapid triage. A cardiology consult should be made immediately to ensure that the patient gets treated within the time frame recommendations. Because MI can be associated with several serious complications, these patients are best managed in an ICU setting.

Hepatobiliary Disease

COMMON DISORDERS

- Autoimmune chronic active hepatitis
- Viral hepatitis Alcoholic hepatitis
- Alcoholic Liver Disease
- Primary biliary cirrhosis
- Primary Sclerosing Cholangitis
- Benign and malignant liver tumors
- Cholangiocarcinoma (bile duct cancer)
- Budd-Chiari syndrome

- Drug-induced hepatotoxicity
- Gallbladder disease

VALUE OF SERUM ENZYMES IN LIVER DISEASES

Quite a large number of enzyme estimations are available which are used to ascertain liver function.

They can be divided into 2 groups

I. Most commonly and routinely done in the laboratory.

II. Not routinely done in the laboratory.

Most commonly and routinely employed in laboratories are two:

A. Serum transaminases (amino transferases), and

B. Serum alkaline phosphatase.

A. Serum Transaminases (Amino transferases)

Interpretations

• Normal ranges for these enzymes are as follows:

– SGOT (aspartate transaminase): 4 to 17 IU/L (7 to 35 units/ml)

– SGPT (alanine transaminase): 3 to 15 IU/ L (6 to 32 units/ml)

• Both these enzymes are found in most tissues, but the relative amounts vary. Heart muscles are richer

in SGOT, whereas liver contains both but more of SGPT.

• Increases in both transaminases are found in liver diseases, with SGPT much higher than SGOT.

• Their determination is of limited value in differential diagnosis of jaundice because of considerable

overlapping.

• But their determination is of extreme use in assessing the severity and prognosis of parenchymal liver

diseases specially acute infectious hepatitis and serum hepatitis. In these two conditions, highest values in thousand units are seen.

• Screening test: Also useful as a screening test in outbreak of infectious hepatitis (viral hepatitis), it is the most sensitive diagnostic index. The increase can be seen in prodromal stage, when jaundice has not appeared clinically. Such cases can be isolated and segregated from others, so that spread of the disease can be checked.

• Very high values are also obtained in toxic hepatitis, due to carbon tetrachloride poisoning. Increases are comparatively less in drug hepatitis (cholestatic) like chloropromazine.

• In obstructive jaundice (extrahepatic) also increases occur, but usually do not exceed 200 to 300 IU/L.

B. **Serum Alkaline Phosphatase**

Alkaline phosphatase enzyme is found in a number of organs, mostly in bones and liver, then in small intestine, kidney and placenta. Placental isoenzyme of alkaline phosphatase is heat-stable.

Interpretations

• Normal range for serum ALP as per King-Armströng method is 3 to 13 KA Units/100 ml (23 to 92 IU/L).

• It is used for many years in differential diagnosis of jaundice. It is increased in both infectious hepatitis (viral hepatitis) and posthepatic jaundice (extrahepatic obstruction) but the rise is usually much greater in cases of obstructive jaundice. Dividing Line which has been suggested is 35 KA units/100 ml. A value higher than 35 KA units/100 ml is strongly suggestive of diagnosis of obstructive jaundice, in which very high figures even up to 200 units or more may be found. There is certain amount of overlapping mostly in the range of 30 to 45 KA Units/100 ml. Very high values are occasionally found in certain liver diseases, e.g. xanthomatous biliary cirrhosis in which there is no extrahepatic obstruction.

• Higher values are also obtained in space-occupying lesions of liver, e.g.

– Abscess

– Primary carcinoma (hepatoma)

– Metastatic carcinoma

– Infiltrative lesions like lymphoma

– Granuloma and amyloidosis.

A diagnostic triad suggests:

• High serum ALP

• Impaired BSP-retension and

• Normal/or almost normal serum bilirubin.

• Serum ALP is found to be normal in haemolytic jaundice.

Mechanism of increase in ALP in liver diseases

Increase in the activity of ALP in liver diseases is not due to hepatic cell disruption, nor to a

failure of clearance, but rather to increased synthesis of hepatic ALP. The stimulus for this increased synthesis in patients with liver diseases has been attributed to bile duct obstruction either extrahepatically by stones, tumours, strictures or intrahepatically by infiltrative disorders or spaceoccupying lesions.

Note

• The relation of the amino transferase to ALP level may provide better evidence than either test alone, as to whether or not the jaundice is cholestatic.

• High ALP with low amino transferase activity is usual in cholestasis and the converse occurs in noncholestatic jaundice.

It is, however, stressed that there are several intrahepatic causes of cholestasis such as primary biliary cirrhosis, acute alcoholic hepatitis and sclerosing cholangitis in which laparotomy is inappropriate. Hence, even after a confident diagnosis of cholestatic jaundice based on the LFTs, further investigation to define the site of obstruction is imperative.

ENZYME TESTS IN DETERMINATION OF MYOCARDIAL INFARCTION.

Before the introduction of serum GOT assay for the investigation of myocardial infarction the heart had been a "biochemically inaccessible" organ. In cases of suspected myocardial infarction when clinical and ECG evidence was equivocal, there was no other means of specifically investigating possible injury to cardiac muscle.

Why Enzyme Diagnosis?

1. 25 to 30 per cent of myocardial infarctions are not diagnosed "antemortem" sometimes.

2. Clinical diagnosis and angiographic studies do not correlate in 25 to 33 per cent of patients.

3. ECG findings may not be helpful if: • Prior left bundle branch block is present.

Old changes exist that may obscure current ECG interpretation.

• Intramural infarctions may not change ECG pattern.

• Diaphragmatic infarctions often missed on ECG.

Enzyme Assays that are Carried out in

Myocardial Infarction

(a) Commonly done:

• Creatine phosphokinase (CK)

• Aspartate transaminase (G-OT)/or (AST)

• Lactate dehydrogenase (LDH)

(b) Other enzymes which have been studied but not commonly done:

• γ-Glutamyl transpeptidase (GGTP)

• Histaminase

• Pseudocholinesterase

1. SERUM GLUTAMATE OXALOACETATE TRANSAMINASE (S-GOT)

Also called as Aspartate transaminase or aminotransferase (AST).

Site: Concentration of the enzyme is very high, in myocardium.

Normal value: Serum activity of S-GOT varies from 4 to 17 IU/L (25oC) (10-35 of original Karmen spectrophotometric units/ml.)

Behaviour in Acute Myocardial Infarction

In acute myocardial infarction, serum activity rises sharply within the first 12 hours, with a peak

level at 24 hours or over and returns to normal within 3 to 5 days.

Remarks

• Level of serum enzyme has been correlated well with prognosis.

– Levels > 350 IU/L usually fatal, (due to massive infarction)

– Levels > 150 IU/L associated with high mortality and

– Levels < 50 IU/L are associated with low mortality.

• Elevation has been noted in absence of any ECG change.

• Highest incidence of abnormal levels occurs on second day of infarction.

• Rise depends on size of the infarction

• Extracardiac factors: Elevation seen in other diseases

e.g. Muscle disease and hepatic diseases. But these can be differentiated clinically and simultaneous

determination of S-GPT. There is no rise of S-GPT in myocardial infarction.

• Reinfarction results in a secondary rise of S-GOT.

2. CREATINE PHOSPHOKINASE: (CPK OR CK)

This enzyme catalyses the following reaction:

Creatine ~ (P) + ADP → Creatine + ATP

The enzyme is also called as creatine kinase.

Site: Found in high concentration in skeletal muscle, myocardium and brain but not found at all in liver and kidney. Small amounts are found in lung, thyroid and adrenal gland. NOT found in

RB cells and its level is not affected by haemolysis.

Normal value: Serum activity varies from 4 to 60 IU/L

Behaviour in Acute Myocardial Infarction

After myocardial infarction, serum value is found to increase after about 6 hours, reaches a peak level in 24 to 30 hours, and returns to normal level in 2 to 4 days (usually in 72 hours).

Remarks

• Studies suggested that serum CK activity is a more sensitive indicator in early stage of myocardial ischaemia.

• Potentially more useful in subendocardial infarction.

• No increase in activity noted in heart failure and coronary insufficiency.

• Magnitude of elevation was found to be greater than that observed with G-OT or LDH.

Note

• Storage: There is 50 per cent loss of serum CK activity after 6 hours at room temperature and 24 hours at refrigerated temperature. Hence, all determinations of serum CK activity should be done on fresh blood samples.

2. ALDOLASE

Aldolase is necessary for glycolysis in muscle as a "rapid response" pathway for production of adenosine triphosphate, independent of tissue oxygen.

Aldolase catalyses the conversion of fructose 1,6-diphosphate into dihydroxyacetone phosphate and glyceraldehyde 3-phosphate, an important reaction in the glycolytic breakdown of glucose to

lactate in muscle.

Aldolase is a tetramer whose primary structure depends upon the tissue from which it was synthesized (liver, muscle, brain). The brain form of aldolase has, because of its preponderance in white cells, been suggested to be a leukemia marker, but this is not confirmed.

Elevated values are found in muscle diseases, such as Duchenne muscular dystrophy, dermatomyositis, polymyositis, and limb-girdle dystrophy

Reference Values

0-16 years: <14.5 U/L

> or =17 years: <7.7 U/L

Interpretation

The highest levels of aldolase are found in progressive (Duchenne) muscular dystrophy. Lesser elevations are found in dermatomyositis, polymyositis, and limb-girdle dystrophy. In dystrophic conditions causing hyperaldolasemia, the increase in aldolase becomes less dramatic as muscle mass decreases.

Aldolase increases in myocardial infarction in a time pattern similar to the aspartate aminotransferase.Increases are also associated with acute viral hepatitis, but levels are normal or slightly elevated in chronic hepatitis, portal cirrhosis, and obstructive jaundice.Elevations may also be seen with gangrene, prostate tumors, trichinosis, some carcinomas metastatic to the liver, some chronic leukemias, some blood dyscrasias, and delirium tremens

3. LACTATE DEHYDROGENASE (LDH)

LDH catalyses the reversible conversion of pyruvic acid (PA) and lactic acid (LA).

Normal value: Normal serum LDH activity ranges from 60 to 250 IU/L (120-500 units/ml, original Karmen

spectrophotometric method). Behaviour in Acute Myocardial Infarction In acute myocardial infarction, serum activity rises within 12 to 24 hours, attains peak at 48 hours (2 to 4 days) reaching about 1000 IU/L and then return gradually to normal from 8^{th} to 14th day.

Remarks

• The peak rises in S-LDH is roughly proportional to the extent of injury to the myocardial tissue.

• S-LDH elevation may persist for more than a week after CPK and S-GOT levels have returned to normal

levels.

• S-LDH level > 1500 IU/L in acute myocardial infarction suggests a grave prognosis.

Disadvantage

The enzyme is relatively non-specific for myocardial tissue. It is so widespread in body cells that coexistent disease processes in other organs may cause elevations. Thus, S-LDH levels are raised in: carcinomatosis, acute leukaemias, granulocytic leukaemia, pulmonary infarction, renal necrosis, muscle diseases, etc. Less pronounced S-LDH increases are seen in inflammatory hepatic disorders.

Precaution: Red blood cells are rich in LDH, hence avoid haemolysis. Haemolysed samples should not be assayed.

ENZYMES OF PANCREATIC ORIGIN

1. **SERUM AMYLASE**

There are problems in methodology and numerical, results of assay by one procedure cannot easily be

converted by a factor to those obtained by another procedure and IU are difficult to apply.

Many laboratories use:

1. A very quick and rapid amyloclastic method for rapid diagnosis.

2. Saccharogenic method: Which is more accurate (Somogy's method).

Normal value: By Somogy method: 80 to 180 Somogy units/100 ml.

Interpretation

• Acute pancreatitis: Serum amylase assay is the investigation of choice in the diagnosis of Acute pancreatitis. Serum enzyme activity > 1000 units seen within 24 hours returns to normal within 3 days. Also urinary amylase increases and persists a little longer than serum activity.

• In other diseases: As amylase is secreted in the parotid glands, raised serum values not exceeding 1000 units, are usually found in Mumps and other forms of parotitis and also when there is salivary duct stone. This may be of value occasionally in differential diagnosis of – Meningoencephalitis and – In facial swellings of other causes.

• A raised serum amylase though not usually exceeding 500 units is often found in other acute abdominal catastrophes like – Perforated peptic ulcer, – Intestinal obstruction.

• After administration of opiates: Raised values may be seen.

• Macroamylasemia: In some individuals, a form of amylase with a high molecular weight occurs in the

circulation. It cannot pass the glomerular filter and consequently accumulates in the bloodstream. Macroamylasemiashould be suspected when there is (a) an increase in serum amylase and (b) no increase in urinary amylase output. Macroamylase can be formed by combination of ordinary serum amylase with an antibody. It can probably result from polymerization of the enzyme molecule.

2. SERUM LIPASE

Serum Lipase assay is more specific in pancreatic disorders and remains raised for longer periods. But it is not valuable in practice because of the absence of quick assay methods. The lipolytic activity of the serum may be determined by the amount of "olive-oil emulsion" hydrolysed by a given quantity of serum in a given time at 37oC. Values for Lipase can be expressed as the amount of 0.05 M NaOH required to neutralise the FA produced by one ml of serum (Cherry-Crandall). A colorimetric assay has also been designed (Seligman and Nachlas).

Normal Value

• By titrimetric method: 0.06 to 1.02 ml of 0.05 (N) Sodium hydroxide.

• By colorimetric assays: 9.0 to 20 m IU. (Seligman and Nachlas).

Remarks: Increase in serum lipase is a reflection of pancreatic disorders. In acute pancreatitis serum lipase activity increases promptly at the time of onset of symptoms, values as high as 2800 U/L having been reported. The subsequent fall is more gradual than in the case of amylase.

Elevated levels persist in some cases 10 to 14 days or longer (less rapid removal from circulation).

• Elevated serum lipase levels also reported in perforated duodenal and peptic ulcers and in intestinal obstruction.

• Moderate increases of serum lipase were found in about 1/3 patients with cirrhosis.

• Provocative Tests with secretin and PZ, have been reported:

– In normal cases duodenal juice amylase is increased and serum level is unaltered.

– In chronic pancreatitis duodenal juice value is unaltered but serum level increases.

EZYMES OF BILIARY TRACT ORIGIN .

The "biliary tract" enzymes (leucine aminopeptidase, y-glutamyltranspeptidase and 5'-nucleotidase) in serum reflect to varying degrees, obstruction, proliferation, inflammation and neoplasia involving the hepatobiliary duct system. Their use is directed towards two purposes as non-electrophoretic assays to evaluate the source of an elevated non-specific alkaline phosphatase and to offer greater sensitivity and specificity for space-occuping lesions in the liver.

CLINICAL SIGNIFICANCE OF ELECTROLYTES.

Sodium measurements are used in the diagnosis and treatment of aldosteronism (excessive secretion of the hormone aldosterone), diabetes insipidus (chronic excretion of large amounts of dilute urine, accompanied by extreme thirst), adrenal hypertension, Addison's disease (caused by

destruction of the adrenal glands), dehydration, inappropriate antidiuretic hormone secretion, or other diseases involving electrolyte imbalance. Potassium measurements are used to monitor electrolyte balance in the diagnosis and treatment of disease conditions characterized by low or high blood potassium levels. Chloride measurements are used in the diagnosis and treatment of electrolyte and metabolic disorders such as cystic fibrosis and diabetic acidosis. The urine electrolytes sodium, potassium and chloride are principally used as nutritional indicators in healthy persons. They are infrequently measured in clinical settings, and when they are it is usually in Intensive/Critical care units. Their measured values are not diagnostic of any disease in and of themselves; rather they can in certain special situations be used to help support the diagnosis of several somewhat rare clinical conditions. The more important use of urinary electrolyte data is for public health studies. Urine sodium data is an important biomarker of dietary sodium intake.

KARPAGAM ACADEMY OF HIGHER EDUCATION

DEPARTMENT OF BIOCHEMISTRY

II-M.Sc., BIOCHEMISTRY

CLINICAL BIOCHEMISTRY (18BCP302)

MULTIPLE CHOICE QUESTIONS

Questions	A			D	Answer
The most useful test for the diagnosis of acute hemorrhagic pancreatitis during the first few days is:	Urinary lipase test	Serum calcium	Urinary amylase	Serum amylase	Serum amylase
The best test for acute pancreatitis in the presence of mumps is:	A serological test for mumps	Virus isolation	Serum lipase	Urinary amylase	Serum lipase
The slow moving fraction of LDH is typically increased in patients with:	Cerebro vascular accidents	Acute myocardial infarction	Acute pancreatitis	Acute viral hepatitis	Acute viral hepatitis
Which of the following enzyme typically elevated in alcoholism	Serum ALP	Serum GOT	Serum ɤ-GT	Serum acid phosphatise	Serum ɤ-GT
Patients with hepatocellular jaundice, as compared to those with purely obstructive jaundice, tend to have:	Lower serum ALP, LDH and AST activity	Lower serum ALP, higher LDH and AST activity	Higher serum ALP, LDH and AST activity	Higher serum ALP, lower LDH and AST activity	Lower serum ALP, higher LDH and AST activity
If results of the serum bilirubin, serum ALP, LDH and AST	Serum ALT	Serum 5'-nucleotidase	Serum protein electrophoresis	Serum pseudocholinesterase	Serum 5'-nucleotidase
Which enzyme estimation will be helpful in differentiating the elevated serum ALP found in obstructive jaundice as well as bone disorders?	Serum AST	Serum ALT	Serum LDH	Serum ɤ-GT	Serum ɤ-GT
Cardiac muscle contains which of the following CK isoenzyme?	BB only	MM and BB only	MM, BB and MB all three	MM and MB only	MM and MB only
Liver and skeletal muscle disorder are characterised by a disproportionate increase in which of the LDH isoenzyme fraction?	LDH-1	LDH-5	LDH-3 and LDH-4	LDH-2 and LDH-3	LDH-5
On the third day following onset of acute myocardial infarction which enzyme estimation will have the best predictive value?	Serum AST	Serum CK	Serum ALT	Serum LDH	Serum LDH
Serum ASt activity is not characteristically elevated as the result of:	Myocardial infarction	Passive congestion of liver	Muscular dystrophies	Peptic ulcer	Peptic ulcer
On which day following acute myocardial infarction the estimation of serum AST will be of greatest significance?	First day	Second day	Third day	Fourth day	Second day
In which diseases of the following organs, isoenzymes LDH-1 and LDH-2 will be released in plasma?	Kidney, red blood cells, liver	Heart, kidney, red cells,	Heart, kidney, liver	Heart, lungs, brain	Heart, kidney, red cells,
Rise of which serum enzyme activity 4-8 hours after acute myocardial infarction is characteristically seen?	AST	ALT	LDH	CK	CK
Which serum enzyme activity will be useful to establish myocardial infarction if the patient is seen after three weeks of suspected attack?	AST	LDH	ɤ-GT	CK	ɤ-GT
An increase in LDH-5 isoenzyme is seen in the following except:	Acute hepatitis	Muscular dystrophies	Breast carcinoma	Pulmonary embolism	Pulmonary embolism
In a case of jaundice, there is no trace of bile pigments in urine, the most probable diagnosis is:	Infections hepatitis	Obstructive jaundice	Serum hepatitis	Haemolytic jaundice	Haemolytic jaundice
The following enzyme activities are often increased along with the diseases as mentioned in each:	UDP—Glucuronyl transferase and Gilbert's	Gammaglutamyl oxidase and viral hepatitis	cholestatic and obstructive jaundice	Gammaglutamyl transferase and obstructive jaundice	Alkaline phosphatase and cholestatic and obstructive jaundice
Jaundice is clinically detected in sclerae when serum bilirubin concentration reaches above:	0.5 to 1 mg/100 ml	1 to 2 mg/100 ml	2 to 3 mg/100 ml	3 to 4 mg/100 ml	2 to 3 mg/100 ml
When jaundice results from hepatitis, the unconjugated fraction of total serum bilirubin is usually:	At least 50%	Less than 50%	50 to 85%	85 to 90%	Less than 50%
Patients with hepatocellular jaundice as compared to those with purely obstructive jaundice, tend to have:	phosphatase, LDH and ALT activity	phosphatase activity, lower LDH and ALT activity	phosphatase activity, LDH and ALT activity,	phosphatase activity, higher LDH and ALT activity	Lower serum alkaline phosphatase activity, higher LDH and ALT activity
If results of the serum bilirubin, alkaline phosphatase, LDH and ALT determination suggest obstructive jaundice, the ideal confirmatory test would be:	Serum ICD	Protein electrophoresis	Serum 5-Nucleotidase	Serum OCT	Serum 5-Nucleotidase
The slow moving fraction of LDH isoenzyme LD5 (M4) is typically elevated in patients with:	Myocardial infarction	Cerebrovascular accident (stroke)	Pancreatitis	Hepatitis	Hepatitis
Drugs can cause jaundice by all of the following mechanisms except:	By causing haemolysis	By selective toxic effects on kupffer cells of liver	By causing intrahepatic cholestasis	bilirubin for albumin binding site	By competition with bilirubin for albumin binding site
Prothrombin time in obstructive jaundice:	Normal	Decreases	Becomes normal after vit K injection	Increases after vit K injection,	Becomes normal after vit K injection
Prothrombin time in parenchymal disease of the liver:	Normal	Decreases	Increases	Becomes normal after parenteral vit K injection	Increases
Overflow aminoaciduria is one of the abnormalities observed in patients with:	Acute hepatic necrosis	Obstructive jaundice	Cholecystitis	Nephrotic syndrome	Acute hepatic necrosis
In which of the following conditions the plasma activities of both ALP and GGT are likely to be increased:	Carcinoma of prostrate	In trimester of normal pregnancy	Osteomalacia	Alcoholic cirrhosis	Alcoholic cirrhosis
Increased unconjugated bilirubin is found in all of the following except:	hemolytic anemia	Crigglar Najjar syndrome	Gilbert's syndrome	Dubin-Johnson syndrome	Dubin-Johnson syndrome
In the liver, a substantial proportion of the activity of the following enzyme is membrance bound:	Aspartate Aminotransferase	Alanine Aminotransferase	Lactate dehydrogenase	Alkaline phosphatase	Alkaline phosphatase
In primary dehydration ECF becomes:	Isotonic	Hypotonic	Hypertonic	None of the above	Hypertonic
In pure salt depletion (secondary dehydration) ECF becomes:	Hypertonic	Hypotonic	Isotonic	None of the above	Hypotonic
In pure water depletion, the fluid to be administered IV is:	Isotonic saline	1/2 Normal saline	1/3 Normal Saline	5 per cent Glucose solution	5 per cent Glucose solution
Urine normally contains NaCl.	2 to 6 gm/litre .	3–8 gm/litre	4–8 gm/litre	6 to 16 gm/litre	6 to 16 gm/litre
Aldosterone is synthesized in the	zona glomerulos	zona fasciculata.	zona reticularis.	Medulla	zona glomerulos
Glucocorticoids regulate their own secretion by inhibiting the pituitary secretion of	corticotropin-releasing hormone.	adrenocorticotropic hormone.	melanocyte-stimulating hormone.	renin.	adrenocorticotropic hormone.
The majority of cases of Cushing's syndrome are caused by	adrenal carcinom	ectopic ACTH production.	adrenal adenoma.	pituitary adenoma.	pituitary adenoma.
cortisol, very low serum ACTH, no suppression of cortisol in response to low-dose DST, and unilateral uptake of iodocholesterol, the most likely diagnosis would be	adrenal carcinom	ectopic ACTH production.	adrenal adenoma.	pituitary adenoma.	adrenal adenoma.
In an adult female patient with classic Cushing's disease (caused by a pituitary adenoma), the preferred treatment is	mitotane 3 g tid.	cyproheptadine 6 mg qid.	bilateral adrenalectomy.	resection of the pituitary tumor.	mitotane 3 g tid.
Which of the following signs or symptoms are seen in both primary and secondary adrenal insufficiency?	Hyperpigmentation	Normal aldosterone secretion	Normal response to the rapid ACTH-stimulation test	Weakness	Weakness
Patients who will be taking glucocorticoids long term should be warned about all the following except	insomnia often occur when starting treatment.	osteoporosis and glaucoma for which they must be monitored.	medical identification stating that they are on chronic steroid	decrease dose during times of increased stress.	that patients may need to decrease dose during times of increased stress.
Myocardial infrction is best differentiated from acute myocardial ischaemia by	Duration of chest pain	History	Electrocardiogram	Troponn and cardiac enzyme level	Troponn and cardiac enzyme level
Heart attack occurs when there is blood clotting in	renal arteries	mesenteric arteries	hepatic arteries	coronary arteries	coronary arteries
Myocardial infarction is also known as	diabetes	heart attack	cholesterol	hypertension	heart attack
The pathogenesis of acute myocardial infarction includes which of the following?	Endothelial injury associated with one or more coronary	Endothelial dysfunction preceding atherosclerosis	Coronary endothelial fatty streak preceding atherosclerotic	All of the above	All of the above
Myocardial ischemia differs from or is related to myocardial infarction in which of the following ways?	Ischemia follows infarction.	Ischemia is not reversible, whereas infarction is.	Infarction is not reversible, whereas ischemia is.	Ischemia is characterized by an increase in myocardial	Infarction is not reversible, whereas ischemia is.
Which of the following correctly characterizes prognosis following MI?	Since an anterior wall MI involves a smaller area than	The most important prognostic indicator following MI is left	A low-risk patient following MI is one who is 70 years of	Prognosis following MI is better after the second or	The most important prognostic indicator following MI is left ventricular function.
Which of the following correctly characterizes the clinical presentation of MI?	Chest pain is an infrequent finding in patients with an	All patients with MI have chest pain.	Chest pain is the sole diagnostic determinant of MI.	Chest pain may occur together with diaphoresis,	Chest pain may occur together with diaphoresis, nausea or vomiting, and shortness of breath.
Serum lactate dehydrogenase is not raised in	iron deficiency	Viral hepatitis	Myocardial infraction	Carcinomatosis	iron deficiency
Following myocardial infaraction, the earliest serum enzyme to rise is	Creatine kinase	SGOT	SGPT	LDH	Creatine kinase
Creatine kinase is not found chiefly in	Myocardium	Brain	Muscle	Prostate	Prostate
Following myocardial infraction, the last serum enzyme to return to normal is	Creatine kinase	SGOT	SGPT	LDH	LDH
The following isoenzyme of lactate dehydrogenase is raised in myocardial failure	LDH1	LDH2	LDH1 and 2	LDH5	LDH1 and 2

Following isoenzyme of creatine kinase in serum is raised in myocardial failure	CK-BB	CK-MM	CK-MB	CK unaltered	CK-MB
After myocardial infraction, peak elevation of serum LDH is likely at	12 hours	24 hours	3 days	7 days	3 days
After myocardial infraction, peak elevation of serum creatine kinase is likely at	3 hours	6 hours	24 hours	12 hours	24 hours
Following myocardial infraction, serum creatine kinase returns to normal in	24 hours	3 days	5 days	7 days	3 days
Following myocardial infraction, serum LDH returns to normal in	24 hours	3 days	5 days	7 days	7 days
In hemolytic jaundice, the direct bilirubin fraction of bilirubin	Increases	Decreases	Remains the same	None of the above	Increases
In hepatocellular jaundice, urine bilirubin is	increased	usually absent	Remains the small amount	None of the above	Remains the small amount

UNIT-IV

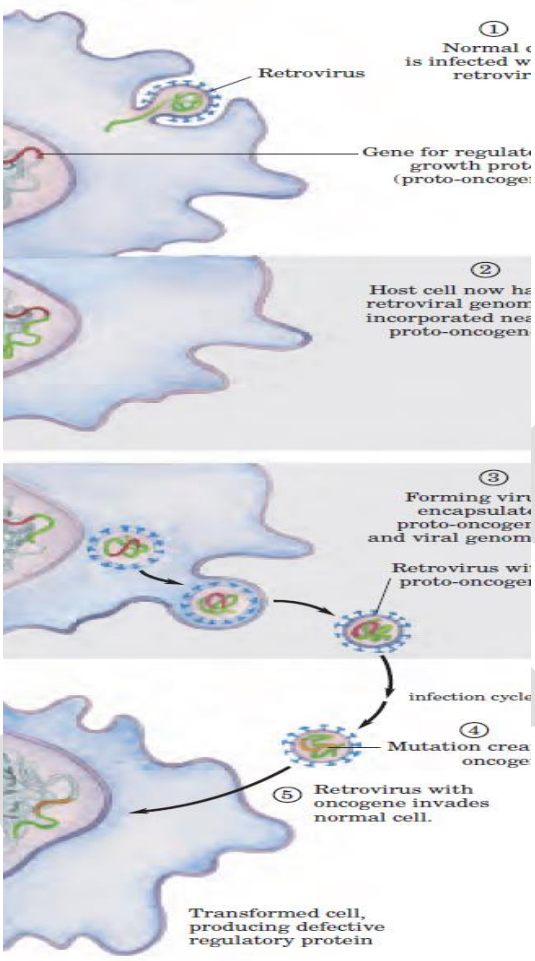
SYLLABUS

Oncogenes and cell cycle, Etiology-Free radical induced cancer. Free radical scavengers. Antioxidants in disease prevention. Benign and malignant types- Different stages of cancer progression- Cancer Markers. Therapy-Chemotherapy, 4 R's of radiotherapy, Diagnosis and prognosis of various cancers.

Tumors and cancer are the result of uncontrolled cell division. Normally, cell division is regulated by a family of extracellular growth factors, proteins that cause resting cells to divide and, in some cases, differentiate. Defects in the synthesis, regulation, or recognition of growth factors can lead to cancer.

Oncogenes Are Mutant Forms of the Genes for Proteins That Regulate the Cell Cycle

Oncogenes were originally discovered in tumor-causing viruses, then later found to be closely similar to or derived from genes in the animal host cells, protooncogenes, which encode growth-regulating proteins. During viral infections, the DNA sequence of a protooncogene is sometimes copied by the virus and incorporated into its genome .At some point during the viral infection cycle, the gene can become defective by truncation or mutation. When this viral oncogene is expressed in its host cell during a subsequent infection, the abnormal protein product interferes with normal regulation of cell growth, sometimes resulting in a tumor.



Proto-oncogenes can become oncogenes without a viral intermediary. Chromosomal rearrangements, chemical agents, and radiation are among the factors that can cause oncogenic mutations. The mutations that produce oncogenes are genetically dominant; if either of a pair of chromosomes contains a defective gene, that gene product sends the signal "divide" and a tumor will result. The oncogenic defect can be in any of the proteins involved in communicating the "divide" signal. We know of oncogenes that encode secreted proteins, growth factors,

transmembrane proteins (receptors), cytoplasmic proteins (G proteins and protein kinases), and the nuclear transcription factors that control the expression of genes essential for cell division (Jun, Fos).

Free radical induced cancer.

Reactive oxygen and nitrogen species, such as super oxide anion, hydrogen peroxide, hydroxyl radical, and nitric oxide and their biological metabolites also play an important role in carcinogenesis. ROS induce DNA damage, as the reaction of free radicals with DNA includes strand break base modification and DNA protein cross-links. Numerous investigators have proposed participation of free radicals in carcinogenesis, mutation, and transformation; it is clear that their presence in biosystem could lead to mutation, transformation, and ultimately cancer. Induction of mutagenesis, the best known of the biological effect of radiation, occurs mainly through damage of DNA by the HO. Radical and other species are produced by the radiolysis, and also by direct radiation effect on DNA, the reaction effects on DNA. The reaction of HO. Radicals is mainly addition to double bond of pyrimidine bases and abstraction of hydrogen from the sugar moiety resulting in chain reaction of DNA. These effects cause cell mutagenesis and carcinogenesis lipid peroxides are also responsible for the activation of carcinogens.

Free radical scavengers

An antioxidant is a molecule stable enough to donate an electron to a rampaging free radical and neutralize it, thus reducing its capacity to damage. These antioxidants delay or inhibit cellular damage mainly through their free radical scavenging property. These low-molecular-weight

antioxidants can safely interact with free radicals and terminate the chain reaction before vital molecules are damaged. Some of such antioxidants, including glutathione, ubiquinol, and uric acid, are produced during normal metabolism in the body.Other lighter antioxidants are found in the diet. Although there are several enzymes system within the body that scavenge free radicals, the principle micronutrient (vitamins) antioxidants are vitamin E (α-tocopherol), vitamin C (ascorbic acid), and B-carotene. The body cannot manufacture these micronutrients, so they must be supplied in the diet.

Early research on the role of antioxidants in biology focused on their use in preventing the oxidation of unsaturated fats, which is the cause of rancidity.Antioxidant activity could be measured simply by placing the fat in a closed container with oxygen and measuring the rate of oxygen consumption. However, it was the identification of vitamins A, C, and E as antioxidants that revolutionized the field and led to the realization of the importance of antioxidants in the biochemistry of living organisms.The possible mechanisms of action of antioxidants were first explored when it was recognized that a substance with antioxidative activity is likely to be one that is itself readily oxidized.Research into how vitamin E prevents the process of lipid peroxidation led to the identification of antioxidants as reducing agents that prevent oxidative reactions, often by scavenging ROS before they can damage cells.

Antioxidant defense system

Antioxidants act as radical scavenger, hydrogen donor, electron donor, peroxide decomposer, singlet oxygen quencher, enzyme inhibitor, synergist, and metal-chelating agents. Both

enzymatic and nonenzymatic antioxidants exist in the intracellular and extracellular environment to detoxify ROS.

Mechanism of action of antioxidants

Two principle mechanisms of action have been proposed for antioxidants.[40] The first is a chain- breaking mechanism by which the primary antioxidant donates an electron to the free radical present in the systems. The second mechanism involves removal of ROS/reactive nitrogen species initiators (secondary antioxidants) by quenching chain-initiating catalyst. Antioxidants may exert their effect on biological systems by different mechanisms including electron donation, metal ion chelation, co-antioxidants, or by gene expression regulation.[41]

Levels of antioxidant action

The antioxidants acting in the defense systems act at different levels such as preventive, radical scavenging, repair and de novo, and the fourth line of defense, i.e., the adaptation.

The first line of defense is the preventive antioxidants, which suppress the formation of free radicals. Although the precise mechanism and site of radical formation in vivo are not well elucidated yet, the metal-induced decompositions of hydroperoxides and hydrogen peroxide must be one of the important sources. To suppress such reactions, some antioxidants reduce hydroperoxides and hydrogen peroxide beforehand to alcohols and water, respectively, without generation of free radicals and some proteins sequester metal ions.

Glutathione peroxidase, glutathione-s-transferase, phospholipid hydroperoxide glutathione peroxidase (PHGPX), and peroxidase are known to decompose lipid hydroperoxides to corresponding alcohols. PHGPX is unique in that it can reduce hydroperoxides of phospholipids integrated into biomembranes. Glutathione peroxidase and catalase reduce hydrogen peroxide to water.

The second line of defense is the antioxidants that scavenge the active radicals to suppress chain initiation and/or break the chain propagation reactions. Various endogenous radical-scavenging antioxidants are known: some are hydrophilic and others are lipophilic. Vitamin C, uric acid, bilirubin, albumin, and thiols are hydrophilic, radical-scavenging antioxidants, while vitamin E and ubiquinol are lipophilic radical-scavenging antioxidants. Vitamin E is accepted as the most potent radical-scavenging lipophilic antioxidant.

The third line of defense is the repair and de novo antioxidants. The proteolytic enzymes, proteinases, proteases, and peptidases, present in the cytosol and in the mitochondria of mammalian cells, recognize, degrade, and remove oxidatively modified proteins and prevent the accumulation of oxidized proteins.

The DNA repair systems also play an important role in the total defense system against oxidative damage. Various kinds of enzymes such as glycosylases and nucleases, which repair the damaged DNA, are known.

There is another important function called adaptation where the signal for the production and reactions of free radicals induces formation and transport of the appropriate antioxidant to

the right site.

ENZYMATIC

Types of antioxidants

Cells are protected against oxidative stress by an interacting network of antioxidant enzymes.Here, the superoxide released by processes such as oxidative phosphorylation is first converted to hydrogen peroxide and then further reduced to give water. This detoxification pathway is the result of multiple enzymes, with superoxide dismutases catalyzing the first step and then catalases and various peroxidases removing hydrogen peroxide.

Superoxide dismutase

Superoxide dismutases (SODs) are a class of closely related enzymes that catalyze the breakdown of the superoxide anion into oxygen and hydrogen peroxide.SOD enzymes are present in almost all aerobic cells and in extracellular fluids. There are three major families of superoxide dismutase, depending on the metal cofactor: Cu/Zn (which binds both copper and zinc), Fe and Mn types (which bind either iron or manganese), and finally the Ni type which binds nickel. In higher plants, SOD isozymes have been localized in different cell compartments. Mn-SOD is present in mitochondria and peroxisomes. Fe-SOD has been found mainly in chloroplasts but has also been detected in peroxisomes, and CuZn-SOD has been localized in cytosol, chloroplasts, peroxisomes, and apoplast.

In humans (as in all other mammals and most chordates), three forms of superoxide dismutase are present. SOD1 is located in the cytoplasm, SOD2 in the mitochondria, and SOD3

is extracellular. The first is a dimer (consists of two units), while the others are tetramers (four subunits). SOD1 and SOD3 contain copper and zinc, while SOD2 has manganese in its reactive center.

Catalase

Catalase is a common enzyme found in nearly all living organisms, which are exposed to oxygen, where it functions to catalyze the decomposition of hydrogen peroxide to water and oxygen.Hydrogen peroxide is a harmful by-product of many normal metabolic processes: to prevent damage, it must be quickly converted into other, less dangerous substances. To this end, catalase is frequently used by cells to rapidly catalyze the decomposition of hydrogen peroxide into less reactive gaseous oxygen and water molecules. All known animals use catalase in every organ, with particularly high concentrations occurring in the liver.

Glutathione systems

The glutathione system includes glutathione, glutathione reductase, glutathione peroxidases, and glutathione S-transferases. This system is found in animals, plants, and microorganisms. Glutathione peroxidase is an enzyme containing four selenium-cofactors that catalyze the breakdown of hydrogen peroxide and organic hydroperoxides. There are at least four different glutathione peroxidase isozymes in animals. Glutathione peroxidase 1 is the most abundant and is a very efficient scavenger of hydrogen peroxide, while glutathione peroxidase 4 is most active with lipid hydroperoxides. The glutathione S-transferases show high activity with lipid peroxides. These enzymes are at particularly high levels in the liver and also serve in

detoxification metabolism.

NONENZYMATIC

Ascorbic acid

Ascorbic acid or "vitamin C" is a monosaccharide antioxidantfound in both animals and plants. As it cannot be synthesized in humans and must be obtained from the diet, it is a vitamin. Most other animals are able to produce this compound in their bodies and do not require it in their diets. In cells, it is maintained in its reduced form by reaction with glutathione, which can be catalyzed by protein disulfide isomerase and glutaredoxins. Ascorbic acid is a reducing agent and can reduce and thereby neutralize ROS such as hydrogen peroxide.In addition to its direct antioxidant effects, ascorbic acid is also a substrate for the antioxidant enzyme ascorbate peroxidase, a function that is particularly important in stress resistance in plants.

Glutathione

Glutathione is a cysteine-containing peptide found in mostforms of aerobic life. It is not required in the diet and is instead synthesized in cells from its constituent amino acids. Glutathione has antioxidant properties since the thiol group in its cysteine moiety is a reducing agent and can be reversibly oxidized and reduced. In cells, glutathione is maintained in the reduced form by the enzyme glutathione reductase and in turn reduces other metabolites and enzyme systems as well as reacting directly with oxidants. Due to its high concentration and central role in maintaining the cell's redox state, glutathione is one of the most important cellular antioxidants.In some organisms, glutathione is replaced by other thiols, such as by mycothiol in the actinomycetes, or

by trypanothione in the kinetoplastids.

Melatonin

Melatonin, also known chemically as N-acetyl-5-methoxytryptamine, is a naturally occurring hormone found in animals and in some other living organisms, including algae.Melatonin is a powerful antioxidant that can easily cross cell membranes and the blood–brain barrier.Unlike other antioxidants, melatonin does not undergo redox cycling, which is the ability of a molecule to undergo repeated reduction and oxidation. Melatonin, once oxidized, cannot be reduced to its former state because it forms several stable end-products upon reacting with free radicals. Therefore, it has been referred to as a terminal (or suicidal) antioxidant.

Tocopherols and tocotrienols (Vitamin E)

Vitamin E is the collective name for a set of eight related tocopherols and tocotrienols, which are fat-soluble vitamins with antioxidant properties. Of these, α-tocopherol has been most studied as it has the highest bioavailability, with the body preferentially absorbing and metabolizing this form. It has been claimed that the α-tocopherol form is the most important lipid-soluble antioxidant, and that it protects membranes from oxidation by reacting with lipid radicals produced in the lipid peroxidation chain reaction. This removes the free radical intermediates and prevents the propagation reaction from continuing. This reaction produces oxidized α-tocopheroxyl radicals that can be recycled back to the active reduced form through reduction by other antioxidants, such as ascorbate, retinol, or ubiquinol.

Uric acid

Uric acid accounts for roughly half the antioxidant ability of plasma. In fact, uric acid may have substituted for ascorbate in human evolution. However, like ascorbate, uric acid can also mediate the production of active oxygen species

Antioxidants in disease prevention.

Antioxidants can decrease oxidative stress induced carcinogenesis by a direct scavenging of ROS and/or by inhibiting cell proliferation secondary to the protein phosphorylation. B-carotene may be protective against cancer through its antioxidant function, because oxidative products can cause genetic damage. Thus, the photo protective properties of B-carotene may protect against ultraviolet light induced carcinogenesis. Immunoenhancement of B-carotene may contribute to cancer protection. B-carotene may also have anticarcinogenic effect by altering the liver metabolism effects of carcinogens.Vitamin C may be helpful in preventing cancer. The possible mechanisms by which vitamin C may affect carcinogenesis include antioxidant effects, blocking of formation of nitrosanimes, enhancement of the immune response, and acceleration of detoxification of liver enzymes. Vitamin E, an important antioxidant, plays a role in immunocompetence by increasing humoral antibody protection, resistance to bacterial infections, cell-mediated immunity, the T-lymphocytes tumor necrosis factor production, inhibition of mutagen formation, repair of membranes in DNA, and blocking micro cell line formation.Hence vitamin E may be useful in cancer prevention and inhibit carcinogenesis by the stimulation of the immune system. The administration of a mixture of the above three antioxidant reveled the highest reduction in risk of developing cardiac cancer.

BENIGN AND MALIGNANT TYPES

Benign Tumor

A benign tumor is not a cancerous tumor. Unlike cancer tumors, a non cancerous tumor is unable to spread throughout the body. A non malignant tumor can be serious if they are pressing a primary nerve, a main artery, or compresses brain matter. Overall, benign tumors respond well to treatment and the prognosis is usually favorable.

Some suspected causes of benign tumors include a traumatic injury at the tumor location, chronic inflammation (or long-term stress that leads to inflammation), an undetected infection, or diet.

Most Common Types of Benign Tumors

- Adenomas (epithelial tissue that covers the organs and glands)
- Meningiomas (brain and spinal cord)
- Fibromas or fibroids (connective tissue of any organ – most commonly found in the uterus)
- Papillomas (skin, breast, cervix, and mucus membranes)
- Lipomas (fat cells)
- Nevi (moles)
- Myomas (muscle tissue)

- Hemangiomas (blood vessels and skin)
- Neuromas (nerves)
- Osteochondromas (bones)

Depending on the location and size of a benign tumor, treatment might not be necessary. Doctors will monitor it, track patient symptoms and do tests at specific intervals. Benign tumors are often surrounded by a protective "sac" – a mechanism performed by your immune system – that segregates it from the rest of your body and enables it to be easily removed.

Malignant Tumor

If your doctor determines that you have a malignant tumor, that means the mass is cancerous. The word malignant is Latin for "badly born." This type of tumor has the ability to multiply uncontrollably, to metastasize (spread) to various parts of the body and invade surrounding tissue.

Malignant tumors are formed from abnormal cells that are highly unstable and travel via the blood stream, circulatory system, and lymphatic system. Malignant cells do not have chemical adhesion molecules to anchor them to the original growth site that benign tumors possess.

There are many suspected causes of cancer – some are widely accepted by the medical community while others are not. Obesity, smoking, alcohol consumption, poor diet, environmental pollution, heavy metal exposure, and household toxins are a few culprits that may

lead to cancer in your body.

Most Common Types of Malignant Tumors

Sarcomas (connective tissues such as muscle, tendon, fat, and cartilage)

Carcinomas (organs and gland tissue such as the breast, cervix, prostate, lung, and thyroid)

Malignant tumors may not have symptoms initially and the first indication that something isn't right may be the detection of a painless lump. These types of tumors are "elastic," which enables them to grow fairly large before they are detected.

As they grow and begin to press against organs, blood vessels and nerves, pain and general soreness at the site may occur.

Different stages of cancer progression-

- **Stage 0**: carcinoma in situ, abnormal cells growing in their normal place ("in situ" from Latin for "in its place").
- **Stage I**: cancers are localized to one part of the body. Stage I cancer can be surgically removed if small enough.
- **Stage II**: cancers are locally advanced. Stage II cancer can be treated by chemo, radiation, or surgery.
- **Stage III**: cancers are also locally advanced. Whether a cancer is designated as Stage II or Stage III can depend on the specific type of cancer; for example, in Hodgkin's Disease, Stage II indicates affected lymph nodes on only one side of the diaphragm, whereas Stage III

indicates affected lymph nodes above and below the diaphragm. The specific criteria for Stages II and III therefore differ according to diagnosis. Stage III can be treated by chemo, radiation, or surgery.

- **Stage IV**: cancers have often metastasized, or spread to other organs or throughout the body. Stage IV cancer can be treated by chemo, radiation, or surgery.

Cancer Markers.

They are also called as tumor index substances. They are factors released from the tumor cells, which could be detected in blood and therefore indicate the presence of the tumor in the body. They are useful for the following purposes.

a. For follow-up of cancer and to monitor the effectiveness of the therapy and also to detect the recurrence of the tumor

b. To facilitate detection of cancer. The presence of tumor marker suggests the diagnosis, but caution is to be taken to rule out other non-malignant conditions.

c. For prognosis. Serum level of the marker may indicate roughly the tumor load, which in turn

indicates whether the disease is curable or not.

d. For localization. Experimentally it is shown that radiolabeled antibodies against the marker will be fixed on the tissues producing the marker.

e. Precautions: Tumor markers are sometimes elevated in nonmalignant conditions. Not every tumor will cause a rise in the level of its associated marker, especially in the early stages of some cancers. When a marker is used for cancer screening or diagnosis, the physician must confirm a positive test result by using imaging studies, tissue biopsies, and other procedures.

Clinically Important Tumor Markers

Name	*Serum level increased in*
Oncofetal Products Alpha fetoprotein (AFP)	Hepatoma, germ cell cancers
Carcinoembryonic antigen (CEA)	Colorectal, gastrointestinal, and lung cancer
Carbohydrate Antigens CA-125	Ovarian cancer of epithelial origin
Tissue Antigens Tissue polypeptide antigen	General cancer load
Enzymes Alkaline phosphatase (ALP) Bone secondaries Placental type ALP (Regan)	Lung, seminoma
Prostatic acid phosphatase (PAP)	Prostate cancer
Prostate specific	Prostate cancer Antigen (PSA)
Neuron Specific Enolase	Neuro-endocrine tumors
Hormones and their Metabolites	
Beta-hCG	Choriocarcinoma
Calcitonin	Medullary thyroid carcinoma
Big ACTH	Lung oat cell cancer
Vasoactive intestinal polypeptide (VIP)	Apudomas (Amine precursor uptake decarboxylation-omas)
Vanillyl mandelic acid (VMA)	Pheochromocytoma and neuroblastoma
Hydroxy indole acetic acid	Carcinoid syndrome
Tissue Catabolic Product	
Hydroxy proline	Bone metastasis
Serum Proteins Immunoglobulins (Ig)	Multiple myeloma, macroglobulinemia
Bence-Jones proteins (in urine)	Multiple myeloma

Therapy-Chemotherapy, radiotherapy, hormonal therapy and phytotherapy.

Surgery and radiotherapy are most effective to reduce the initial tumor load. These are the prime modalities of treatment in solid tumors. Chemotherapy is the sheet anchor of therapy in leukemias, advanced lymphomas, choriocarcinoma and other widely disseminated malignancies. The effectiveness of cytotoxic drugs is directly proportional to the doubling time of the tumors, and is inversely proportional to the number of cancer cells. Cytotoxic drugs affect all the cells

which are in the dividing phase. Rapidly dividing normal cells (gastrointestinal tract, hematopoietic system, hair follicles, gonads) are also affected by chemotherapeutic drugs, leading to toxicity. In fact, pharmacological dose and toxic dose usually overlap in the case of these drugs.

Cell destruction by cytotoxic drug follows the first order kinetics, that is, it reduces a constant percentage and not a constant number of cancer cells.

The same dose, which reduces the cancer cells from 108 to 107, is required to reduce them from 103 to 102. Therefore, it is difficult to eradicate the residual cancer cells by chemotherapy. These are lysed by the immune mechanisms, when a complete cure is achieved. Some important anticancer drugs are listed in Tables below

Name	*Type*	*Mode of action*
Methotrexate	Folic acid analogue	Competitive inhibitor of dihydrofolate reductase. THFA is required for nucleotide synthesis
6-Mercapto purine	Purine analogue	Inhibits the conversion of IMP to AMP
6-thio guanine	Purine analogue	Inhibits the conversion of IMP to AMP
Cyclophosphamide	Alkylating agent	Cross linking of bases of DNA; inhibition of strand separation
MitomycinC	Antibiotic	Cross bridges are formed between DNA base pairs
Actinomycin D	Antibiotic	Intercalates with guanine bases of DNA; prevents transcription
Vincristine and Vinblastine	Alkaloids from Vinca rosea	Interferes with assembly of cytoskeleton and inhibits Stathmokinesis (spindle movement)
Adriamycin	Anthracyclins	Topo-isomerase mediated breaks in DNA
Etoposide	Podophyllotoxin	Stabilises topo-isomerase-II-DNA cleavage complexes
Camptothecin		Modifies function of topo-isomerase-I to DNA breaking agent
Cisplatin	Platinum compound	Forms intrastrand DNA adducts
Imatinib	Monoclonal antibody	Tyrosine kinase inhibitor
Fluorouracil (FU)	Pyrimidine analog	Inhibits thymidylate synthase

Plants are considered as important resources for researchers to prove and develop new drugs. Generally, using plants in the treatment of cancer has a long history and thus plants have been primary resources for producing traditional drugs effective in the treatment of cancer.

After identifying new proteins that had important regulatory effects on the development of the tumors cell cycle, research in isolating molecules from plants and other natural organisms approved that plants are important resources for synthesis inhibitors that have potential to develop production of anticancer drugs.

Moreover, researchers have reported a large number of plant species that have been used in the treatment of cancer since ancient times, and today, the tendency toward the use and evaluation of therapeutic effects of plants and their compounds as potential anticancer drugs are increasing. So at the present time, more than half of the used anticancer drugs are derived from natural resources like plants, microorganisms, and sea creatures.

The mechanisms by which these drugs act on cancer cells are mostly unclear. However, the role of oxidative stress in the induction of cancer and antioxidants in the prevention and treatment of cancer is obvious, and most plants are good sources of antioxidants. Numerous studies have suggested that most cancers are diet related. Furthermore, the risks of most kinds of cancers can be reduced by dietary changes. In this regard, the studies in different countries have suggested that the prevalence of cancer is less in people who eat higher amounts of fruits or vegetables that have antioxidant activity.

There are more than 25 000 phytochemicals in different plants that often have biological effects.11 Diets rich in herbal resources provide necessary essential vitamins and minerals to the body. The ability of the molecules present in medicinal plants to bond therapeutic sites holds promise for achievement of natural products and compounds from plants that are effective on cancer with low toxicity on healthy tissues.

Angiogenesis is also a natural condition that controls the formation of new blood vessels from the available vessels and has a crucial role in cancer development. This process, unlike cancer, is the basis of several physiologic processes like embryonic development, reproduction cycle, and wound healing.

DIAGNOSIS OF VARIOUS CANCERS.

Lab Tests

High or low levels of certain substances in your body can be a sign of cancer. So, lab tests of the blood, urine, or other body fluids that measure these substances can help doctors make a diagnosis. However, abnormal lab results are not a sure sign of cancer. Lab tests are an important tool, but doctors cannot rely on them alone to diagnose cancer.

Imaging Procedures

Imaging procedures create pictures of areas inside your body that help the doctor see whether a tumor is present. These pictures can be made in several ways:

CT Scan:

An x-ray machine linked to a computer takes a series of detailed pictures of your organs. You may receive a dye or other contrast material to highlight areas inside the body. Contrast material helps make these pictures easier to read.

Nuclear scan:

For this scan, you receive an injection of a small amount of radioactive material, which is sometimes called a tracer. It flows through your bloodstream and collects in certain bones or organs. A machine called a scanner detects and measures the radioactivity. The scanner creates pictures of bones or organs on a computer screen or on film. Your body gets rid of the radioactive substance quickly. This type of scan may also be called radionuclide scan.

Ultrasound:

An ultrasound device sends out sound waves that people cannot hear. The waves bounce off tissues inside your body like an echo. A computer uses these echoes to create a picture of areas inside your body. This picture is called a sonogram.

MRI:

A strong magnet linked to a computer is used to make detailed pictures of areas in your body. Your doctor can view these pictures on a monitor and print them on film.

PET scan:

For this scan, you receive an injection of a tracer. Then, a machine makes 3-D pictures that show where the tracer collects in the body. These scans show how organs and tissues are working.

X-rays:

X-rays use low doses of radiation to create pictures of the inside of your body.

Biopsy

In most cases, doctors need to do a biopsy to make a diagnosis of cancer. A biopsy is a procedure in which the doctor removes a sample of tissue. A pathologist then looks at the tissue under a microscope to see if it is cancer. The sample may be removed in several ways:

With a needle: The doctor uses a needle to withdraw tissue or fluid.

With an endoscope: The doctor looks at areas inside the body using a thin, lighted tube called an endoscope. The scope is inserted through a natural opening, such as the mouth. Then, the doctor uses a special tool to remove tissue or cells through the tube.

With surgery: Surgery may be excisional or incisional.

In an excisional biopsy, the surgeon removes the entire tumor. Often some of the normal tissue around the tumor also is removed.

KARPAGAM ACADEMY OF HIGHER EDUCATION
DEPARTMENT OF BIOCHEMISTRY
II-M.Sc., BIOCHEMISTRY
CLINICAL BIOCHEMISTRY (18BCP302)
MULTIPLE CHOICE QUESTIONS

Unit IV

S.No	Questions	Option A	Option B	Option C	Option D	Answer
1	Cancer cells are	BHK	Veo	HL-8	Hela cells	Hela cells
2	Cancer cells can easily be destroyed by radiations due to	fast mutation	rapid cell division	lack of mutation	lack of oxygen	rapid cell division
3	Cancer of β lymphocytes is called	Sarcoma	Melanoma	myeloma	carcinoma	myeloma
4	The basic difference between a cancer cell and a normal cell is	cancer cells divide continuously but normal cells do not divide	normal cell is bigger than cancer cells	normal cells are immortal but cancer cells are mortal	cancer cells divide do not differentiate like normal cells	cancer cells divide do not differentiate like normal cells
5	Carcinogens	may not occur naturally	are all man made	are all caused due to ionic radiation	may be caused due to tar of tobacco smoke	may be caused due to tar of tobacco smoke
6	Any agent that causes cancer is called	mutagen	carcinogen	oncogene	None of above	carcinogen
7	Which of the following is the most commonly mutated oncogene in cancer?	p53	abl	ras	myc	ras
8	In any discussion involving cancer with a patient, there are usu	staging	grade	anaplasia	dysplasia	staging
9	Tumours are classified by:	The person who discovered them.	Their ability to spread.	Their weight	The tissue or cell of origin.	Their ability to spread.
10	*TNM stands for:*	*Temperature, Metabolism, Nut*	*Tumour, Nerve, Metastases*	*Tumour, Node, Metastases.*	*Tumour, Nodule, Metastases*	*Tumour, Node, Metastases.*
11	*Tumour markers are:*	*Signs of infection*	*Related to genetics*	*Chemicals that can be detected i*	External growths	*Chemicals that can be detected in the blood*
12	One difference between cancer cells and normal cells is that c	are unable to synthesize DNA.	are unable to synthesize DN/	continue to divide even when they	cannot function properly because they ar	continue to divide even when they are tightly packed together.
13	The term for a mass of cells growing out of control is _____.	a benign tumor	a malignant tumor	metastasis	All of the above are correct.	a malignant tumor
14	What term is used to indicate the ability of a cancer to invade other parts of the body and to produce secondary tumours?	Carcinogenesis	Apoptosis	Metastasis	Mutagenesis	Metastasis
15	What is the term used to indicate the growth of new blood vessels?	Biosynthesis	Angiogenesis	Apoptosis	Metastasis	Angiogenesis
16	Which molecules are involved in the anchoring of cells to an extracellular matrix?	Integrins	Interleukins	Angiostatin	Cyclins	Integrins
17	Cancer cells:	Divide uncontrollably and then	Are particularly sensitive to e	Divide uncontrollably and are imi	Are impossible to grow in culture	Divide uncontrollably and are immortal
18	Cancer cells are not:	Contact inhibited	Transplantable	Invasive	De-differentiated	Contact inhibited
19	A cancer cell is said to be _____ if it is shown that the disease will spread when injected into a healthy, susceptible animal.	Contact inhibited	Transplantable	Benign	Invasive	Transplantable
20	A cancer that spreads is termed:	Benign	Carcinogenic	Metastatic	Mutagenic	Metastatic
21	A cytogenetic diagnosis of chronic myeloid leukemia is made by identification of:	Barr bodies	Viral infection	Promyelocytes	The Philadelphia chromosome	The Philadelphia chromosome
22	Melanoma is a type of	skin cancer	lung cancer	tesicular cancer	blood cancer	skin cancer
23	The virus implicated in cancer is	Herpes virus	HIV	Influenza virus	Epstein Barr virus	Epstein Barr virus
24	Malignant tumors _____.	are surrounded by connective tissue	can be easily removed surgically	remain in one place as a well-defined mass of cells	can travel and begin growing in distant body locations	can travel and begin growing in distant body locations
25	Oncogenes are the cancer causing genes in the cells but they d	proto oncogenes	tumour promoters	tumour suppressor genes	transposons or jumping genes	tumour suppressor genes
26	Which one of the following genes is involved in the conversion of proto-oncogenes into oncogenes causing cancer?	metastasis genes	angiogenesis genes	transposons	tumour suppressor genes	tumour suppressor genes
27	About 50% of all human cancers may involve an abnormal or	oncogene	proto-oncogene.	p53 gene.	BRCA-1 gene	oncogene
28	The P53 protein normally promotes	DNA repair.	tumor formation	cell division	apoptosis	apoptosis
29	The P53 gene is especially prone to	point mutation	chromosomal rearrangement	loss.	none of the above	point mutation
30	What is acquired during the progression of ALL tumors?	loss of the RB gene	mutations	the ability to synthesize mitogens	activation of tumor suppressors	mutations
31	A proto-oncogene can become an oncogene when:	It is shut off	It is translocated next to a highly expressed gene	Growth factors decrease cell division rate	A person is exposed to pesticides	It is translocated next to a highly expressed gene
32	Genes that normally prevent cell division are:	Tumor suppressors	Transcription factors	Proto-oncogenes	Growth factors	Tumor suppressors
33	Loss of tumor suppression in a cell usually results from:	Cytokine activation of a tumor	A translocation of a tumor su	An inversion involving a tumor suppressor gene	A deletion of a tumor suppressor gene	A deletion of a tumor suppressor gene
34	*BRCA*1 and *BRCA*2 mutations:	Are X-linked	Are incompletely penetrant	Result from translocations	Occur only in malignant breast tumors	Are incompletely penetrant
35	The BRAC1 gene is involved in regulating:	Cell division	Cell death	DNA repair	DNA replication	DNA repair
36	In cancer cells, oncogenes cause:	an excess of Cyclin D which gives an uncontrollable cell division.	an excess of p53 inhibitors so apoptosis does not occur.	Both a and b are correct	Neither a nor b are correct	Both a and b are correct
37	Patients with familial retinoblastoma carry a germline mutation in one copy of the Rb gene. Potential mechanisms for inactivation of the other allele in a retinoblastoma tumor arising in one of these patients include:	loss of the normal chromosome 13	Mitotic crossing over	an independent point mutation	all of the above	all of the above
38	Which of the following is an example of a condition caused by a mutation in a single gene?	Colon cancer	Heart disease	AIDS	Cystic fibrosis	Cystic fibrosis
39	A man presents with a tumor that is found to carry a translocation of chromosomes 9 and 22. This is most characteristic of which one of the following?	Retinoblastoma	Li–Fraumeni syndrome	Chronic myelogenous leukemia	Soft tissue sarcoma	Chronic myelogenous leukemia
40	In order to enter the cell cycle a cell must be stimulated from outside. What type of molecule provides this stimulation?	Cyclins	Cyclin-dependent kinases	Cytokines and growth factors	Tyrosine kinases	Tyrosine kinases
41	In which phase of the cell cycle is DNA replicated?	G1 phase	S phase	G2 phase	M phase	S phase
42	The passage of a cell through the stages of the cell cycle is controlled by protein kinases that phosphorylate many different proteins at appropriate times. What are these protein kinases called?	Cdk activating kinases	Cyclin-dependent kinases	Cyclins	Tyrosine kinases	Cyclin-dependent kinases
43	Cyclin dependent kinases which control progression through cell cycle checkpoints are fully activated by which of the following:	binding to cyclins.	phosphorylation by Cdk activ	binding to cyclin, plus phosphory	phosphorylation by a tyrosine kinase.	binding to cyclin, plus phosphorylation by a Cdk activating protein kinase
44	Passage through which checkpoint is the step which commits the cell to proceed through to mitosis and cell division?	G1 to S	S to G2	G2 to M	M to G1	G1 to S
45	The MPF protein complex turns itself off by	activating a process that destroys cyclin component.	activating an enzyme that stimulates cyclin.	binding to chromatin.	exiting the cell.	activating a process that destroys cyclin component.
46	Fibroblasts have receptors for this substance on their plasma r	PDGF	MPF	protein kinase	cyclin	PDGF
47	_____ begins when pairs of sister chromatids align	Anaphase	Metaphase	Prophase	Telophase	Metaphase
48	The primary growth phase of a cell is the	G0	G1	G2	M	G1
49	Which cellular organelles are involved in the initiation of the a	endoplasmic reticulum	lysosomes	mitochondria	peroxisomes	mitochondria
50	What roles in regulating the intrinsic pathway of apoptosis are played by the Bcl-2 protein family members Bax and Bcl-2?	Bax inhibits apoptosis while Bc	Bax stimulates apoptosis while Bcl-2 inhibits apoptosis.	Both Bax and Bcl-2 inhibit apoptosis.	Both Bax and Bcl-2 stimulate apoptosis.	Bax stimulates apoptosis while Bcl-2 inhibits apoptosis.
51	The triggering of the intrinsic pathway of apoptosis involves a balance between pro-apoptotic and anti-apoptotic proteins. Which of the following is anti-apoptotic?	Bax.	Bad.	Bcl-2	Cytochrome C	Bcl-2
52	Apoptosis is classified as	programmed cell death	non-programmed cell death	accidental cell death	mitotic cell death	programmed cell death
53	Necrosis it is death:	of cells due to metabolic disorders	of parenchymatous cells only	of cells and tissues in a living org	programmed, genetically determined death of cells	of cells and tissues in a living organism
54	Anti-apoptotic proteins are	Bcl 2 & Bc1 x	Apaf – 1	Bax & Bim	Bim & Bid	Bcl 2 & Bc1 x
55	Which source of carcinogens is associated with approximately 30% of all cancer deaths?	UV radiation	tobacco	X-ray and gamma radiation	viruses	tobacco
56	Tumor marker for primary hepatocellular carcinoma are all except	Alpha feto protein	Alpha 2 macroglobulin	PIVKA-2	Neurotensin	Alpha 2 macroglobulin
57	The most common cancer in males is:	lung cancer	colorectal cancer	prostate cancer	leukemia	prostate cancer
58	The most common cancer in females is:	non-Hodgkin lymphoma	lung cancer	ovarian cancer	breast cancer	breast cancer
59	____ percent of all cancers are related to tobacco smoke.	80	90	70	60	80
60	What DNA virus has been linked to a type of human cancer?	hepatitis B virus	human papillomavirus	Epstein-Barr virus	All of these are correct	All of these are correct
61	Which of the following is a correct sign of possible malignant melanoma?	uniform color of a mole	irregular border of a mole	symmetrical appearance of a mole	a mole with a diameter of 2mm	irregular border of a mole

62	The PAP smear is a test for _____ cancer.	colon	cervical	breast	ovarian	cervical
63	_____ is an X-ray study of the breast used to detect tumors too small to be felt.	Sigmoidoscopy	Mammography	Tomography	Chemotherapy	Mammography
64	Sigmoidoscopy is a test for _____ cancer.	breast	colon	cervical	brain	colon
65	The standard methods of treatment for cancer are _____.	surgery	radiation	chemotherapy	All of these are correct	All of these are correct
66	Gene therapy targeting the germ-line is…	Heritable	Not heritable	Sometimes heritable	Unrelated to heritability	Heritable
67	In gene therapy, in order to be successful, the healthy gene inserted into a target cell must…	Take over and kill the defective gene	Be inserted manually into the cell's mitochondria	Become attached to the cell's mRNA molecules	Be able to make the correct amount of the protein needed	Be able to make the correct amount of the protein needed
68	When was the first gene therapy patient treated?	1988	1990	1993	1999	1990

UNIT - V

SYLLABUS

Pathophysiology of – hypothalamus and pituitary (dwarfism, Klienfelter syndrome, adenoma, galactorrhea, amenorrhea). Pathophysiology of thyroid cretinism, myxodema, hashimoto's (autoimmune thyroid disorder), hypo- and hyperparathyroidism, bone (osteopenia and osteoporosis), adrenal (Cushing syndrome and Addison's disease) Pancreas (IDDM and NIDDM) and gonads (cystic ovaries, endometriosis, hypogonadism, cryptorchidis and testicular carcinoma).

Pathophysiology of – hypothalamus and pituitary

The thyroid gland is the largest classic endocrine organ. Its disorders are very frequent. If diabetes mellitus, which regularly ranks among metabolic diseases, is not considered, the thyroid gland disorders make about 4/5 of the total number of endocrinopathies. The thyroid gland disorders are much more frequent in women than in men (7:1).

Thyrotropic hyperpituitarism (pituitary hyperthyroidism, secondary hyperthyroidism) is very rare. It is caused by macroadenoma (thyrotropic adenoma) of thyrotrophs which overproduces TSH (TSH-induced hyperthyroidism). In the patients the clinical symptoms of thyrotoxicosis are present, however, they are usually milder than in primary (peripheral) hyperthyroidism.

Adenohypophyseal hypofunctions

Decreased ability of the anterior lobe of the pituitary gland to produce one or more tropic hormones is called hypopituitarism. Insufficient secretion of only one pituitary hormone (**isolated hypopituitarism**, monohormonal hypopituitarism, monotropic hypopituitarism) occurs seldom and it is mostly STH deficiency.

Somatotropic hypopituitarism

In the patients with the somatotropic hypopituitarism. STH deficiency is present or this hormone is totally absent. In about one third of cases it is **an isolated** GH deficiency. However, in the rest of the patients the deficiency of GH is **combinated** with the deficiency of

gonadotropins.

In adults, STH deficiency is usually cryptic. Its presence in adults does not seem to be inevitable. But, the consequences of STH deficiency and replacement in adults are still being explored. Physiological production of GH is needed only in children during the whole period of body growth, i.e., till the epiphyseal growth plates are closed. Insuficient STH production in childhood or youth before epiphyseal closure leads to impaired growth and short stature, respectivelly gives rise to the origin of **hyposomatotropic dwarfism** (pituitary dwarfism, pituitary nanism). However, it is more often a consequence of hypothalamic GHRH deficiency than a consequence of primary disorder of STH production by pituitary somatotropes. There are two forms of hyposomatotropic dwarfism: hypothalamic and pituitary.

Hypothalamic dwarfism is usually caused by isolated STH deficiency, while **pituitary dwarfism** is mostly characterized by combinated disorder, e.g., by STH deficiency and gonadotropin deficiency. The cause of the both mentioned forms of hyposomatotropic dwarfism can be found only in about 35% of affected children. It may be an organic disorder, e.g., tumor, cyst, aneurysm, trauma, or other pathological process endamaging the cells of competent endocrine active tissue of hypothalamus or adenohypophysis.

In about 65% of patients the cause of GH deficiency can not be found (idiopathic hyposomatotropic dwarfism). The both forms of hyposomatotropic dwarfism are necessary to differ from those forms of dwarfism in which plasma GH concentration is normal or even increased. The following forms of dwarfism must be distinguished:

1. Nanism caused by long-term severe **nutritional insufficiency**.
2. Nanism caused by some **chronic diseases**, e.g., malabsorption or chronic inflammatory intestine disease, chronic renal disease (renal nanism), severe congenital heart disease (cardial nanism), severe pulmonary disease, and severe haematological disease.
3. Dwarfism caused by **insensitivity to GH** at the level of GH receptors. This disorder is due to absent or defective GH receptors. It is also widely known as **Laron-type dwarfism**, which probably represents only one form of insensitivity to STH (familial form of short stature). Due to STH receptors disorder IGF I (somatomedin C) is not produced in hepatocytes and in cells of

other tissues. The serum IGF I concentration is low and does not increase in response to injection of human GH. Abnormalities of DNA restriction fragment length in some of these patients are consistent with defects in the gene encoding the GH receptor.

Pathophysiology and clinical features of hyposomatotropic dwarfism. The most expressive symptom of this disease is a disorder of body growth. Children with hyposomatotropic hypopituitarism are of a short stature and exhibit growth curves that deviate progressively from normal. In idiopathic hypopituitarism, growth failure may not be obvious until patients are 2 to 4 years old. In retrospect, however, it is often possible to establish that growth failure began in the first few months of life. The growth disorder is most evidently manifested at the onset of puberty when the psychical problems from short stature of the pacient may appear. Retardation or precocious cessation of body growth is the result of **longitudinal bone growth disorder**, while epiphyseal growth plates are open for longer than usual. Therefore, in the patient the slow growth may be prolonged until age 30–40 years. A bone age retardation in relation to chronological age (delayed skeletal maturation) is evident. Closure of the fontanelles and eruption of permanent teeth are delayed.

The final height of hypophyseal dwarf varies from 120 to 150 cm. The stature is, however, usually proportional (the patients exhibit normal body proportions). Overall look, especially facial appearance is infantile for quite a long time. On the contrary, in adulthood the facial appearance is progeric (precociously senile). There is no significant deviation of the patient intelect. In the first several years of life, approximately 10% of children with somatotropic hypopituitarism have hypoglycemic convulsions. An additional 10% or more have asymptomatic fasting hypoglycemia. Hypoglycemia is usually secondary to combined deficiencies of cortisol and GH.

Somatotropic hypopituitarism in children is usually associated with gonadotropin deficiency (combinated hypopituitarism). In that case along with dwarfism also sexual infantilism occurs.

Klinefelter syndrome

Klinefelter syndrome is a genetic condition that results when a boy is born with an extra copy of the X chromosome. Klinefelter syndrome is a common genetic condition affecting males, and

it often isn't diagnosed until adulthood. Klinefelter syndrome may adversely affect testicular growth, resulting in smaller than normal testicles, which can lead to lower production of testosterone. The syndrome may also cause reduced muscle mass, reduced body and facial hair, and enlarged breast tissue. The effects of Klinefelter syndrome vary, and not everyone has the same signs and symptoms.

Most men with Klinefelter syndrome produce little or no sperm, but assisted reproductive procedures may make it possible for some men with Klinefelter syndrome to father children.

Symptoms

Signs and symptoms of Klinefelter syndrome vary widely among males with the disorder. Many boys with Klinefelter syndrome have few noticeable signs, and the condition may go undiagnosed until adulthood. For others, the condition has a noticeable effect on growth or appearance.

- In babies and toddlers – learning to sit up, crawl, walk and talk later than usual, being weaker, quieter and more passive than usual
- In childhood – shyness and low self-confidence, problems with reading, writing, spelling and paying attention, mild dyslexia and/or dyspraxia, low energy levels, difficulty socialising or expressing feelings
- In teenagers – growing taller than expected for the family (with long arms and legs), broad hips, poor muscle tone and slower than usual muscle growth, reduced facial and body hair that starts growing later than usual, a small penis and testicles, enlarged breasts (gynaecomastia)
- In adulthood – inability to have children naturally (infertility) and a low sex drive, in addition to the physical characteristics mentioned above

Health issues in Klinefelter syndrome

Most boys and men with Klinefelter syndrome will not be significantly affected and can live normal, healthy lives. Infertility tends to be the main problem, although there are treatments that can help.

However, men with Klinefelter syndrome are at a slightly increased risk of developing other

health problems, including:

- Type 2 diabetes
- Weak and fragile bones (osteoporosis)
- Cardiovascular disease and blood clots
- Autoimmune disorders (where the immune system mistakenly attacks the body), such as lupus
- An underactive thyroid gland (hypothyroidism)
- Anxiety, learning difficulties and depression – although intelligence is usually unaffected
- Male breast cancer – although this is very rare

These problems can usually be treated if they do occur and testosterone replacement therapy may help reduce the risk of some of them.

Causes of Klinefelter syndrome

Klinefelter syndrome is caused by an additional X chromosome.

This chromosome carries extra copies of genes, which interfere with the development of the testicles and mean they produce less testosterone (male sex hormone) than usual.

The extra genetic information may either be carried in every cell in the body or it may only affect some cells (known as mosaic Klinefelter syndrome).

Klinefelter syndrome isn't directly inherited – the additional X chromosome occurs as a result of either the mother's egg or the father's sperm having the extra X chromosome (an equal chance of this happening in either), so after conception the chromosome pattern is XXY rather than XY.

This change in the egg or sperm seems to happen randomly. If have a son with the condition, the chances of this happening again are very small.

However, the risk of a woman having a son with Klinefelter syndrome may be slightly higher if the mother is over 35 years of age.

Testing for Klinefelter syndrome

Klinefelter syndrome isn't necessarily anything serious, but treatment can help reduce some of the symptoms if necessary.

In many cases, it's only detected if a man with the condition undergoes fertility tests.

It suspect Klinefelter syndrome after a physical examination and they may suggest sending off a sample of blood to check reproductive hormone levels.

The diagnosis can be confirmed by checking a sample of blood for the presence of the extra X chromosome.

Treatments for Klinefelter syndrome

There's no cure for Klinefelter syndrome, but some of the problems associated with the condition can be treated if necessary.

Possible treatments include:

- testosterone replacement therapy
- speech and language therapy during childhood to help with speech development
- educational and behavioural support at school to help with any learning difficulties or behaviour problems, occupational therapy to help with any co-ordination problems associated with dyspraxia
- physiotherapyto help build muscle and increase strength
- psychological support for any mental health issues
- fertility treatment – options include artificial insemination using donor sperm or possibly intra-cytoplasmic sperm injection (ICSI), where sperm removed during a small operation are used to fertilise an egg in a laboratory
- breast reduction surgery to remove excess breast tissue

Pituitary adenomas are tumors that occur in the pituitary gland. Pituitary adenomas are generally divided into three categories dependent upon their biological functioning: benign adenoma, invasive adenoma, and carcinomas. Most adenomas are benign, approximately 35% are invasive and just 0.1% to 0.2% are carcinomas. Pituitary adenomas represent from 10% to 25% of all intracranial neoplasms and the estimated prevalence rate in the general population is approximately 17%. Non-invasive and non-secreting pituitary adenomas are considered to be benign in the literal as well as the clinical sense; however a recent meta-analysis of available research has shown there are to date scant studies – of poor quality – to either support or refute

this assumption.

Adenomas which exceed 10 millimetres (0.39 in) in size are defined as macroadenomas, with those smaller than 10 mm referred to as microadenomas. Most pituitary adenomas are microadenomas, and have an estimated prevalence of 16.7% (14.4% in autopsy studies and 22.5% in radiologic studies). A majority of pituitary microadenomas often remain undiagnosed and those that are diagnosed are often found as an incidental finding, and are referred to as incidentalomas. Pituitary macroadenomas are the most common cause of hypopituitarism, and in the majority of cases they are non-secreting adenomas.

The pituitary is a small gland attached to the base of the brain (behind the nose) in an area called the pituitary fossa or sella turcica. The pituitary is often called the "master gland" because it controls the secretion of most of the hormones in the body. A normal pituitary gland weighs less than 1 gram and is about the size and shape of a kidney bean. The function of the pituitary can be compared to that of a household thermostat. The thermostat constantly measures the temperature in the house and sends signals to the heater to turn it on or off to maintain a steady, comfortable temperature. The pituitary constantly monitors bodily functions and sends signals to remote organs and glands to monitor their function and maintain the appropriate environment. The ideal "thermostat" setting for a body depends on many factors, including level of activity, gender, body composition, etc.

The pituitary is responsible for controlling and coordinating the following:

- ✓ Growth and development
- ✓ Organ function (kidneys, breasts and uterus)
- ✓ Gland function (thyroid, gonads and adrenal glands.

Pituitary adenomas are the fourth most common intracranial tumor after gliomas, meningiomas and schwannomas. A large majority of pituitary adenomas are benign and are relatively slow growing. Adenomas are by far the most common disease affecting the pituitary gland. These tumors most commonly affect people in their 30s or 40s, although they can be diagnosed in children as well. Most of these tumors can be successfully treated. Pituitary tumors can vary in size and behavior. Tumors that produce hormones are called functioning adenomas,

while those that do not are called nonfunctioning adenomas.

Symptoms

Tumors smaller than 10 millimeters are called microadenomas and often secrete anterior pituitary hormones. These smaller, functional adenomas are usually detected earlier because the increased levels of hormones cause abnormal changes in the body. Approximately 50 percent of pituitary adenomas are diagnosed when they are smaller than 5 millimeters in size. Adenomas larger than 10 millimeters (the size of a dime) are called macroadenomas and usually do not secrete hormones. These tumors are often discovered because they produce symptoms by "mass effect," compressing nearby brain or cranial nerve structures.

The symptoms of a pituitary tumor, other than mass effect, generally result from endocrine dysfunction. For example, this dysfunction can cause overproduction of growth hormones, as in acromegaly (gigantism), or underproduction of thyroid hormone, as in hypothyroidism. Hormonal imbalances can impact fertility, menstrual periods, heat and cold tolerance, as well as the skin and body in other ways.

Because of the pituitary gland's strategic location within the skull, tumors of the pituitary can compress important brain structures as they enlarge. The most common circumstance involves compression of the optic nerves leading to a gradual loss of vision. This vision loss usually begins with a deterioration of peripheral vision on both sides.

The presence of three or more of the following symptoms may indicate a pituitary tumor:

- ✓ Vision problems (blurred or double vision, drooping eyelid) Infertility
- ✓ Growth problems
- ✓ Osteoporosis
- ✓ Unexplained weight gain
- ✓ Unexplained weight loss
- ✓ Easy bruising
- ✓ Aching joints
- ✓ Headaches in the forehead area

- ✓ Nausea or vomiting
- ✓ Impaired sense of smell
- ✓ Sexual dysfunction
- ✓ Depression
- ✓ Fatigue.

Hypothalamic amenorrhea

All types of amenorrhea of the hypothalamic origin, with the exception of amenorrhea at anorexia nervosa, rank among this title. They are secondary amenorrhea as caused by various functional or organic disorders of the hypothalamus, which result in disorder of LHRH secretion. Among functional amenorrheas of the hypothalamic origin are included:

• psychogenic amenorrhea after psychic stress;

• amenorrhea at false pregnancy (pseudocyesis, pseudogravidity);

• exercise-induced amenorrhea, which is associated with intense and prolonged physical exertion, such as long-distance running, swimming, gymnastic, and ballet dancing. The patients are always below ideal body weight and have low stores of fat. The mass of fat may be a regulator of LHRH secretion;

• long-term starvation;

• amenorrhea at hyperprolactinemia mediated by decreased hypothalamic dopamine (prolactininhibiting factor – PIF).

Hyperprolactinemia causes amenorrhea by inhibition of LHRH release. Organic causes of hypothalamic amenorrhea can be head trauma, tumor, inflammatory lesion and vascular lesion in the hypothalamic gonadotropin regulating area.

In women hypothalamic hyperprolactinemia is manifested by non-puerperal galactorrhea (continual milk secretion in non-puerperal period), by secondary amenorrhea, and by atrophy of gonads and uterus. The set of these symptoms is called hyperprolactinemic syndrome. From the point of view of endocrinology the clinical picture is the same as at adenohypophyseal hyperprolactinemia. And, therefore, its detailed description is given in the chapter on endocrine disorders of adenohypophysis. If hypothalamic hyperprolactinemia develops post partum, it is

so-called Chiari-Frommel syndrome. It is defined as galactorrhea and amenorrhea persisting more than 6 months post partum in the absence of nursing and without an evident pituitary tumor. Some of these patients probably harbor occult microadenomas stimulated by the hormones of pregnancy that may later become radiologically evident. In about half, menses eventually return over a period of months or years. This syndrome is often connected with psychotic symptoms (depression and somnipathy which may sometimes be similar to those at schizophrenia. If hypothalamic hyperprolactinemia occurs in young women, who are not and have never been pregnant, it is defined as Ahumad-de Castill syndrome (some authors call it Forbers-Albright syndrome).The clinical picture of prolactic hyperpituitarism is characterized especially by the symptoms of hypogonadism and by galactorrhea. It is diferent in both sexes.

In women the main symptom is a disturbance of menstruation (oligomenorrhea or secondary amenorrhea) which is accompanied by infertility. Concentrations of estrogen and progesterone in blood are decreased. Galactorrhea is present in 30–80% of these women and may be related to the duration of gonadal dysfunction. Women with long-standing amenorrhea are less likely to have galactorrhea, which probably reflects prolonged estrogen deficiency. In some women patients (20–30%) other features of estrogen deficiency may occur, such as decreased libido, vaginal dryness, dyspareumia, mastalgia, and hirsutism and tendency to obesity may be also present.

Pathophysiology of thyroid cretinism

Congenital hypothyroidism is a disease of the thyroid gland; this is an endocrine gland located in the anterior neck. The main hormones secreted by the thyroid gland are mostly thyroxine (T4), and a small amount of triiodothyronine (T3). Thyroid hormones have wide-ranging effects on metabolism affecting most organ systems in the body.

The secretion of thyroid hormones is stimulated by thyrotrophin (TSH) which is secreted from the pituitary gland, which is in turn secreted in response to thyrotrophin releasing hormone (TRH), secreted by the hypothalamus. Hypothyroidism refers to an underactive thyroid gland – meaning inappropriately low secretion of thyroid hormones – T4 and T3. It can occur in the

newborn (congenital) or in a previously normal adult (acquired). Hypothyroidism in the newborn may result from absence of or abnormal development of the thyroid gland, destruction of the thyroid gland, failure of stimulation of the thyroid by the pituitary, and/or by defective or abnormal synthesis of thyroid hormones.

Risk Factors for Congenital hypothyroidism (Cretinism)

Numerous genetic syndromes

Underactive pituitary gland (secondary) eg: due to a pituitary tumour or the absence of the pituitary gland

Trauma

Progression of Congenital hypothyroidism (Cretinism)

If untreated, even mild hypothyroidism can lead to severe mental retardation and growth retardation. Development is delayed early on, often indicated by failure to meet normal milestones. The appearance of teeth may be delayed. These problems become more severe as the child ages. Growth failure in terms of body length is noted very early.

Diagnosis

Routine screening of the newborn using a blood-spot, as in the Guthrie test, to detect a high TSH level as an indicator of primary hypothyroidism is efficient and cost-effective, usually done at 5-7 days; cretinism is prevented if T4 is started within the first few months of life.

Prognosis of Congenital hypothyroidism (Cretinism)

Very early diagnosis generally results in a good outcome for the infant, in terms of growth and mental capability. Newborns diagnosed and treated in the first month to month and a half generally develop normal intelligence. Absence of thyroid hormone during early life gives a poor outlook in terms of mental development.

Treatment:

Early diagnosis is imperative. Most of the effects of hypothyroidism are easily reversible. However, critical development of the nervous system takes place in the first few months after birth. Thyroid hormone deficiency may result in irreversible damage to the nervous system with marked mental retardation.

Replacement therapy with thyroxine is the standard approach to treatment of hypothyroidism. Once medication starts, the blood levels of TSH and free T4 are monitored to keep the values within a normal range. Absence of the thyroid and defective thyroxine production are not preventable. Destruction of the thyroid in the fetus may occur if the mother is treated with radioactive iodine for thyroid cancer while she is pregnant.

Myxedema

The thyroid gland, located at the front part of the neck, is responsible for making substances called thyroid hormones that are important for all body cells to work properly.

Myxedema is another term for severely advanced hypothyroidism. This is a condition that occurs when body doesn't produce enough thyroid hormone. The thyroid is a small gland that sits right at the front of neck. It releases hormones that help body regulate energy and control a wide variety of functions. Myxedema is the result of having undiagnosed or untreated severe hypothyroidism.

The term "myxedema" can be used to mean severely advanced hypothyroidism. But it's also used to describe skin changes in someone with severely advanced hypothyroidism. The classic skin changes are: swelling of face, which can include lips, eyelids, and tongue
swelling and thickening of skin anywhere on body, especially in lower legs.

Severely advanced hypothyroidism can lead to what is called a myxedema crisis, a medical emergency. While the term "myxedema coma" used to describe this life-threatening situation, "myxedema crisis" has replaced it, as a comatose state is no longer required to diagnose the condition.

In certain conditions, the thyroid becomes underactive and produces fewer amounts of its hormones, a situation called hypothyroidism. People with hypothyroidism have problems that reflect underactivity of the organs of the body, resulting in symptoms such as fatigue, feeling cold, weight gain, dry skin, and sleepiness. When the levels of thyroid hormones become very low, the symptoms get worse and can result in a serious condition called myxedema coma. Myxedema coma is a rare but life-threatening condition. People with hypothyroidism who are in or near a coma should be taken to an emergency department immediately.

Myxedema, This rare, life-threatening condition is the result of long-term, undiagnosed hypothyroidism. Its signs and symptoms include intense cold intolerance and drowsiness followed by profound lethargy and unconsciousness. A myxedema coma may be triggered by sedatives, infection or other stress on body. If have signs or symptoms of myxedema, need immediate emergency medical treatment.

Symptoms of myxedema crisis can include:

- decreased breathing (respiratory depression)
- lower than normal blood sodium levels
- hypothermia (low body temperature)
- confusion or mental slowness
- shock
- low blood oxygen levels
- high blood carbon dioxide levels
- coma
- seizures

Myxedema crisis can cause death often due to complications from infection, bleeding, or respiratory failure. Hypothyroidism occurs when the thyroid stops functioning properly. This may be caused by: an autoimmune condition, including Hashimoto's disease surgical removal of thyroid

- radiation therapy for cancer
- certain medications, such as lithium or amiodarone (Pacerone)
- iodine deficiency or an excess of iodine
- pregnancy
- immune system medications, like those used in cancer treatment

Myxedema is a result of undiagnosed or untreated severe hypothyroidism. It can also develop when someone stops taking their thyroid medication. It's more common in the elderly and in women. Deposits of chains of sugar molecules (complex mucopolysaccharides) in the skin cause

the skin condition myxedema. These compounds attract water, which lead to swelling. These skin changes are a result of hypothyroidism.

- Myxedema crisis often occurs after a long history of hypothyroidism. It's more common during cold winter months. It can be triggered by any of the following:
- stopping hypothyroid treatment medication
- sudden illness, like heart attack or stroke
- infection
- trauma
- certain drugs that suppress the central nervous system
- exposure to cold
- stress.

Treatment for hypothyroidism involves taking a synthetic version of the T4 hormone known as levothyroxine (Levothroid, Levoxyl). Once T4 hormone levels are restored, symptoms become more manageable, though this may take several weeks.

Hashimoto's diseases

Hashimoto's thyroiditis is an autoimmune disease, a disorder in which the immune system turns against the body's own tissues. In people with Hashimoto's, the immune system attacks the thyroid. This can lead to hypothyroidism, a condition in which the thyroid does not make enough hormones for the body's needs.Causes of Hashimoto's Thyroiditis

The exact cause of Hashimoto's is not known, but many factors are believed to play a role. They include:

People who get Hashimoto's often have family members who have thyroid disease or other autoimmune diseases. This suggests a genetic component to the disease.

Hormones: Hashimoto's affects about seven times as many women as men, suggesting that sex hormones may play a role. Furthermore, some women have thyroid problems during the first year after having a baby. Although the problem usually goes away, as many as 20% of these women develop Hashimoto's years later.

Excessive iodine: Research suggests certain drugs and too much iodine, a trace element required by body to make thyroid hormones, may trigger thyroid disease in susceptible people.

Radiation exposure: Increased cases of thyroid disease have been reported in people exposed to radiation, including the atomic bombs in Japan, the Chernobyl nuclear accident, and radiation treatment for a form of blood cancer called Hodgkin's disease.

Symptoms of Hashimoto's Thyroiditis

Hashimoto's symptoms may be mild at first or take years to develop. The first sign of the disease is often an enlarged thyroid, called a goiter. The goiter may cause the front of neck to look swollen. A large goiter may make swallowing difficult. Other symptoms of an underactive thyroid due to Hashimoto's may include:

- weight gain
- fatigue
- paleness or puffiness of the face
- joint and muscle pain
- constipation
- inability to get warm
- difficulty getting pregnant
- joint and muscle pain
- hair loss or thinning, brittle hair
- irregular or heavy menstrual periods
- depression
- slowed heart rate.

Hypothyroidism is a condition that occurs when thyroid gland doesn't produce enough thyroid hormones. There are many glands in the body, but the thyroid gland is the small, butterfly-shaped organ at the base of neck that makes hormones that regulate metabolism — which affects how the body uses energy — and other processes.

Congenital disease: Some babies are born with a defective thyroid gland or no thyroid gland. In

most cases, the thyroid gland didn't develop normally for unknown reasons, but some children have an inherited form of the disorder. Often, infants with congenital hypothyroidism appear normal at birth. That's one reason why most states now require newborn thyroid screening.

Pituitary disorder: A relatively rare cause of hypothyroidism is the failure of the pituitary gland to produce enough thyroid-stimulating hormone (TSH) — usually because of a benign tumor of the pituitary gland.

Pregnancy: Some women develop hypothyroidism during or after pregnancy (postpartum hypothyroidism), often because they produce antibodies to their own thyroid gland. Left untreated, hypothyroidism increases the risk of miscarriage, premature delivery and preeclampsia — a condition that causes a significant rise in a woman's blood pressure during the last three months of pregnancy. It can also seriously affect the developing fetus.

Iodine deficiency: The trace mineral iodine — found primarily in seafood, seaweed, plants grown in iodine-rich soil and iodized salt — is essential for the production of thyroid hormones. In some parts of the world, iodine deficiency is common, but the addition of iodine to table salt has virtually eliminated this problem in the United States. Conversely, taking in too much iodine can cause hypothyroidism.

Hypoparathyroidism

Hypoparathyroidism is an uncommon condition in which body secretes abnormally low levels of parathyroid hormone (PTH). PTH is key to regulating and maintaining a balance of body's levels of two minerals — calcium and phosphorus. The low production of PTH in hypoparathyroidism leads to abnormally low calcium levels in blood and bones and to an increase of phosphorus in blood. Supplements to normalize calcium and phosphorus levels treat the condition. Depending on the cause of hypoparathyroidism, it 'll likely need to take supplements for life.

Symptoms

Signs and symptoms of hypoparathyroidism can include:

- Tingling or burning (paresthesia) in fingertips, toes and lips
- Muscle aches or cramps in legs, feet, abdomen or face

- Twitching or spasms of muscles, particularly around mouth, but also in hands, arms and throat
- Fatigue or weakness
- Painful menstruation
- Patchy hair loss
- Dry, coarse skin
- Brittle nails
- Depression or anxiety

Causes

Hypoparathyroidism occurs when parathyroid glands don't secrete enough parathyroid hormone. If have four small parathyroid glands situated in neck, behind thyroid gland.

Factors that can cause hypoparathyroidism include:

Post-surgical hypoparathyroidism. This most common cause of hypoparathyroidism develops after accidental damage to or removal of the parathyroid glands during surgery. This surgery might be a treatment for diseases of the thyroid gland, or for throat or neck cancer. Autoimmune disease. Immune system creates antibodies against the parathyroid tissues, trying to reject them as if they were foreign bodies. In the process, the parathyroid glands stop manufacturing their hormone. Hereditary hypoparathyroidism. In this form, either you're born without parathyroid glands or they don't work properly. Some types of hereditary hypoparathyroidism are associated with deficiencies of other hormone-producing glands.

Extensive cancer radiation treatment of face or neck. Radiation can result in destruction of parathyroid glands, as can radioactive iodine treatment for hyperthyroidism, occasionally.

Low levels of magnesium in blood, which can affect the function of parathyroid glands. Normal magnesium levels are required for optimum secretion of parathyroid hormone.

Risk factors

Factors that can increase risk of developing hypoparathyroidism include: Recent neck surgery, particularly if the thyroid was involved. A family history of hypoparathyroidism Having certain

autoimmune or endocrine conditions, such as Addison's disease — which causes adrenal glands to produce too little of its hormones

Complications

Hypoparathyroidism can result in various complications.

Reversible complications

The following are due to low calcium levels, most of which are likely to improve with treatment:

Tetany, These cramp like spasms of hands and fingers can be prolonged and painful. Tetany might also include muscle discomfort and twitches or spasms of the muscles of face, throat or arms. When these spasms occur in throat, they can interfere with breathing, creating a possible emergency, Paresthesias.

These are characterized by odd, tingling sensations or pins and needles feelings in lips, tongue, fingers and toes. Loss of consciousness with convulsions (grand mal seizures).

Malformed teeth, affecting dental enamel and roots.

Impaired kidney function.

Heart arrhythmias and fainting, even heart failure.

Irreversible complications

Accurate diagnosis and treatment might prevent these complications associated with hypoparathyroidism. But once they occur, calcium and vitamin D won't improve them:

Hyperparathyroidism is an excess of parathyroid hormone in the bloodstream due to overactivity of one or more of the body's four parathyroid glands. These glands are about the size of a grain of rice and are located in neck. The parathyroid glands produce parathyroid hormone, which helps maintain an appropriate balance of calcium in the bloodstream and in tissues that depend on calcium for proper functioning. Two types of hyperparathyroidism exist. In primary hyperparathyroidism, an enlargement of one or more of the parathyroid glands causes overproduction of the hormone, resulting in high levels of calcium in the blood (hypercalcemia), which can cause a variety of health problems. Surgery is the most common treatment for primary

hyperparathyroidism.

Secondary hyperparathyroidism occurs as a result of another disease that initially causes low levels of calcium in the body and over time, increased parathyroid hormone levels occur.

Symptoms

Hyperparathyroidism is often diagnosed before signs or symptoms of the disorder are apparent. When symptoms do occur, they're the result of damage or dysfunction in other organs or tissues due to high calcium levels circulating in the blood and urine or too little calcium in bones. Symptoms may be so mild and nonspecific that they don't seem at all related to parathyroid function, or they may be severe. The range of signs and symptoms include:

- Fragile bones that easily fracture (osteoporosis)
- Kidney stones
- Excessive urination
- Abdominal pain
- Tiring easily or weakness
- Depression or forgetfulness
- Bone and joint pain
- Frequent complaints of illness with no apparent cause
- Nausea, vomiting or loss of appetite.

Causes

Hyperparathyroidism is caused by factors that increase the production of parathyroid hormone. The parathyroid glands maintain proper levels of both calcium and phosphorus in body by turning the secretion of parathyroid hormone (PTH) off or on, much like a thermostat controls a heating system to maintain a constant air temperature. Vitamin D also is involved in regulating the amount of calcium in blood.

Normally, this balancing act works well. When calcium levels in blood fall too low, parathyroid glands secrete enough PTH to restore the balance. PTH raises calcium levels by releasing calcium from bones and increasing the amount of calcium absorbed from small

intestine. When blood-calcium levels are too high, the parathyroid glands produce less PTH. But sometimes one or more of these glands produce too much hormone, leading to abnormally high levels of calcium (hypercalcemia) and low levels of phosphorus in blood.

The mineral calcium is best known for its role in keeping teeth and bones healthy. But calcium has other functions. It aids in the transmission of signals in nerve cells, and it's involved in muscle contraction. Phosphorus, another mineral, works in conjunction with calcium in these areas. The disorder can generally be divided into two types based on the cause. Hyperparathyroidism may occur because of a problem with the parathyroid glands themselves (primary hyperparathyroidism) or because of another disease that affects the glands' function (secondary hyperparathyroidism).

Osteopenia

Osteopenia is the term used by doctors to describe low bone density. People with osteopenia have bones that are weaker than normal, but not weak enough to be called osteoporosis. Osteopenia or low bone density is thought to affect around 6.3 million people, and is an early warning sign that should be taking action to reduce risk of developing osteoporosis and breaking a bone in the future.

Causes:

There is usually no single cause. Many factors have an impact on bone strength, and the importance of these factors will be different for each person. Some people are more likely to develop osteopenia because poor bone health runs in the family. Medical conditions and medications can affect risk. For example, osteopenia is more common in people who have coeliac disease (gluten or wheat allergy), and in people who take glucocorticoid medications (steroids) for long periods. Low body weight is another important risk factor; osteopenia is sometimes seen in young female athletes or in people with eating disorders. A natural weakening of the skeleton occurs with age, especially after menopause, so the risk of osteopenia increases greatly at this stage of life. An unhealthy lifestyle and not getting enough of the three important building blocks for good bone health - calcium, vitamin D and exercise - will also increase risk of developing osteopenia.

In prolonged treatment with glucocorticoids, the patient may develop GI ulcers.

Effect on Bones: Glucocorticoids reduce the osteoid matrix of bone, thus favouring **osteoporosis** and there may be excessive loss of calcium from the body.

Osteoporosis" literally means "porous bones." The bones become weaker, increasing the risk of fractures, especially in the hip, spinal vertebrae, and wrist.

Bone tissue is constantly being renewed, and new bone replaces old, damaged bone. In this way, the body maintains bone density and the integrity of its crystals and structure.

Bone density peaks when a person is in their late 20s. After the age of around 35 years, bone starts to become weaker. As age, bone breaks down faster than it builds. If this happens excessively, osteoporosis results.

Signs and symptoms

Bone loss that leads to osteoporosis develops slowly. There are often no symptoms or outward signs, and a person may not know they have it until they experience a fracture after a minor incident, such as a fall, or even a cough or sneeze. Commonly affected areas are the hip, a wrist, or spinal vertebrae. Breaks in the spine can lead to changes in posture, a stoop, and curvature of the spine.

Causes and risk factors

A number of risk factors for osteoporosis have been identified. Some are modifiable, but others cannot be avoided

Treatment of osteoporosis

Treatment aims to, slow or prevent the development of osteoporosis maintain healthy bone mineral density and bone mass prevent fractures reduce pain maximize the person's ability to continue with their daily life. This is done through preventive lifestyle measure and the use of supplements and some drugs.

Cushing's syndrome: (Adrenocortical hyperfunction):

It is often associated with an increase in body fat mainly confined to the head, neck and trunk (turncal obesity and buffalo hump), but spares the limb. It is often associated with a gain in weight. Although a low BMR cannot explain the usual type of obesity, hypothyroidism may be

associated with gain in weight, partly due to water retention in tissues and partly to fat storage; which is evident in particular sites stated above.

Addison's disease

Definition

Addison's disease is a disorder involving disrupted functioning of the part of the adrenal gland called the cortex. This results in decreased production of two important chemicals (hormones) normally released by the adrenal cortex: cortisol and aldosterone.

Description

The adrenals are two glands, each perched on the upper part of the two kidneys. The outer part of the gland is known as the cortex; the inner part is known as the medulla. Each of these parts of the adrenal gland is responsible for producing different types of hormones. Cortisol is a very potent hormone produced by the adrenal cortex. It is involved in regulating the functioning of nearly every type of organ and tissue throughout the body, and is considered to be one of the few hormones absolutely necessary for life.

Cortisol is involved in:

- the very complex processing and utilization of many nutrients, including sugars (carbohydrates), fats, and proteins
- the normal functioning of the circulatory system and the heart
- the functioning of muscles
- normal kidney function production of blood cells
- the normal processes involved in maintaining the skeletal system
- proper functioning of the brain and nerves
- the normal responses of the immune system

Aldosterone, also produced by the adrenal cortex, plays a central role in maintaining the appropriate proportions of water and salts in the body. When this balance is upset, the volume of blood circulating throughout the body will fall dangerously low, accompanied by a drop in blood pressure. Addison's disease is also called primary adrenocortical insufficiency. In other words, some process interferes directly with the ability of the adrenal cortex to produce its

hormones. Levels of both cortisol and aldosterone drop, and numerous functions throughout the body are disrupted. It strikes both men and women of all ages.

Causes and symptoms

The most common cause of Addison's disease is the destruction and/or shrinking (atrophy) of the adrenal cortex. In about 70% of all cases, this atrophy is believed to occur due to an autoimmune disorder. In an autoimmune disorder, the immune system of the body, responsible for identifying foreign invaders such as viruses or bacteria and killing them, accidentally begins to identify the cells of the adrenal cortex as foreign, and destroy them. In about 20% of all cases, destruction of the adrenal cortex is caused by **tuberculosis**. The remaining cases of Addison's disease may be caused by fungal infections, such as **histoplasmosis**, coccidiomycosis, and **cryptococcosis**, which affect the adrenal gland by producing destructive, tumor-like masses called granulomas; a disease called **amyloidosis**, in which a starchy substance called amyloid is deposited in abnormal places throughout the body, interfering with the function of whatever structure it is present within; or invasion of the adrenal glands by **cancer**. The most common symptoms include **fatigue** and loss of energy, decreased appetite, nausea, vomiting, **diarrhea**, abdominal **pain**, weight loss, muscle weakness, **dizziness** when standing, **dehydration**, unusual areas of darkened (pigmented) skin, and dark freckling.

Diagnosis

Many patients do not recognize the slow progression of symptoms and the disease is ultimately identified when a physician notices the areas of increased pigmentation of the skin. Once suspected, a number of blood tests can lead to the diagnosis of Addison's disease. It is not sufficient to demonstrate low blood cortisol levels, as normal levels of cortisol vary quite widely. Instead, patients are given a testing dose of another hormone called corticotropin (ACTH). ACTH is produced in the body by the pituitary gland, and normally acts by promoting growth within the adrenal cortex and stimulating the production and release of cortisol. In Addison's disease, even a dose of synthetic ACTH does not increase cortisol levels.

Treatment

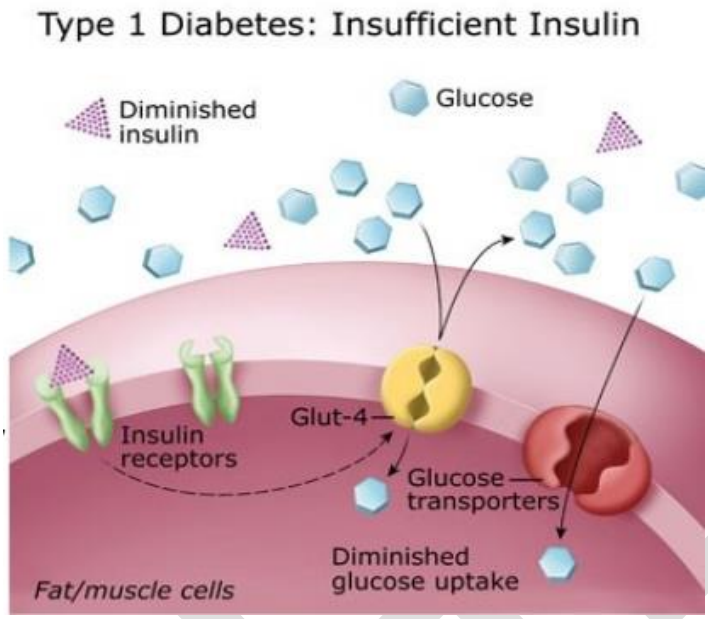
Treatment of Addison's disease involves replacing the missing or low levels of cortisol.

In the case of Addisonian crisis, this will be achieved by injecting a potent form of steroid preparation through a needle placed in a vein (intravenous or IV). Dehydration and salt loss will also be treated by administering carefully balanced solutions through the IV. Dangerously low blood pressure may require special medications to safely elevate it until the steroids take effect.

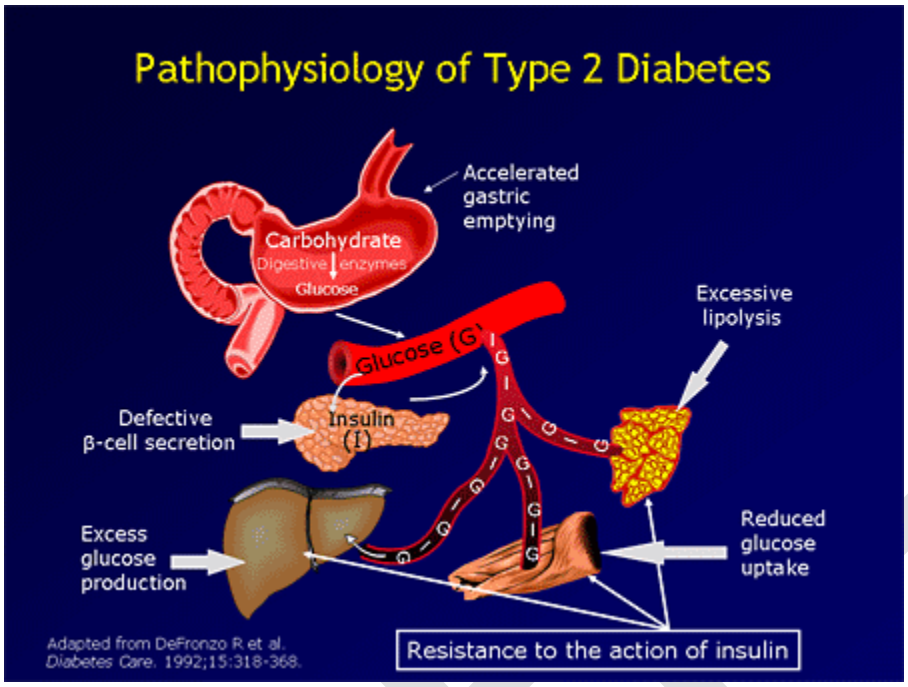
Diabetes mellitus, caused by a deficiency in the secretion or action of insulin, is a relatively common disease: nearly 6% of the United States population shows some degree of abnormality in glucose metabolism that is indicative of diabetes or a tendency toward the condition. There are two major clinical classes of diabetes mellitus: type I diabetes, or insulindependent diabetes mellitus (IDDM), and type II diabetes, or non-insulin-dependent diabetes mellitus (NIDDM), also called insulin-resistant diabetes.

Diabetes:

Amongst the many recent studies highlighting several new benefits of vitamin D there are some that establish its role in preventing diabetes. This is not a surprising revelation as the ubiquitous vitamin D receptors are located in the β-cells of Islet of Langerhans of pancreas. The first evidence of the vit D and diabetes link came when it was noticed, mostly through population studies that insulin dependent Type-1 diabetes (IDDM-1) occurred commonly in areas which receive less sunlight. Observational studies seem to show a link between deficient vit D status of infants and the risk of developing diabetes about 10 to 15 years later. It has been proposed that vitamin D probably stimulates not only the release of insulin but also the expression of insulin receptors. Researchers from Harvard Medical School have shown that low vitamin D levels may be a particular problem for children and teenagers with Type-1 diabetes.



Immune "markers" in type IDM (IDDM): The recent area of interest is the role of "glutamic acid decarboxylase" (GAD) as antigen of potential significance. Recently anti-GAD antibodies have been deomonstrated in most newly diagnosed IDDM (Type I) patients and in predictable first degree relatives. In adults presence of GAD antibody is a "marker" for slow onset Type I DM (IDDM) and helps to differentiate IDDM with age of onset > greater than 35 years and Type II (NIDDM). The term "Latent Autoimmune DM" in adults o "LADA" is now being used for such patients.



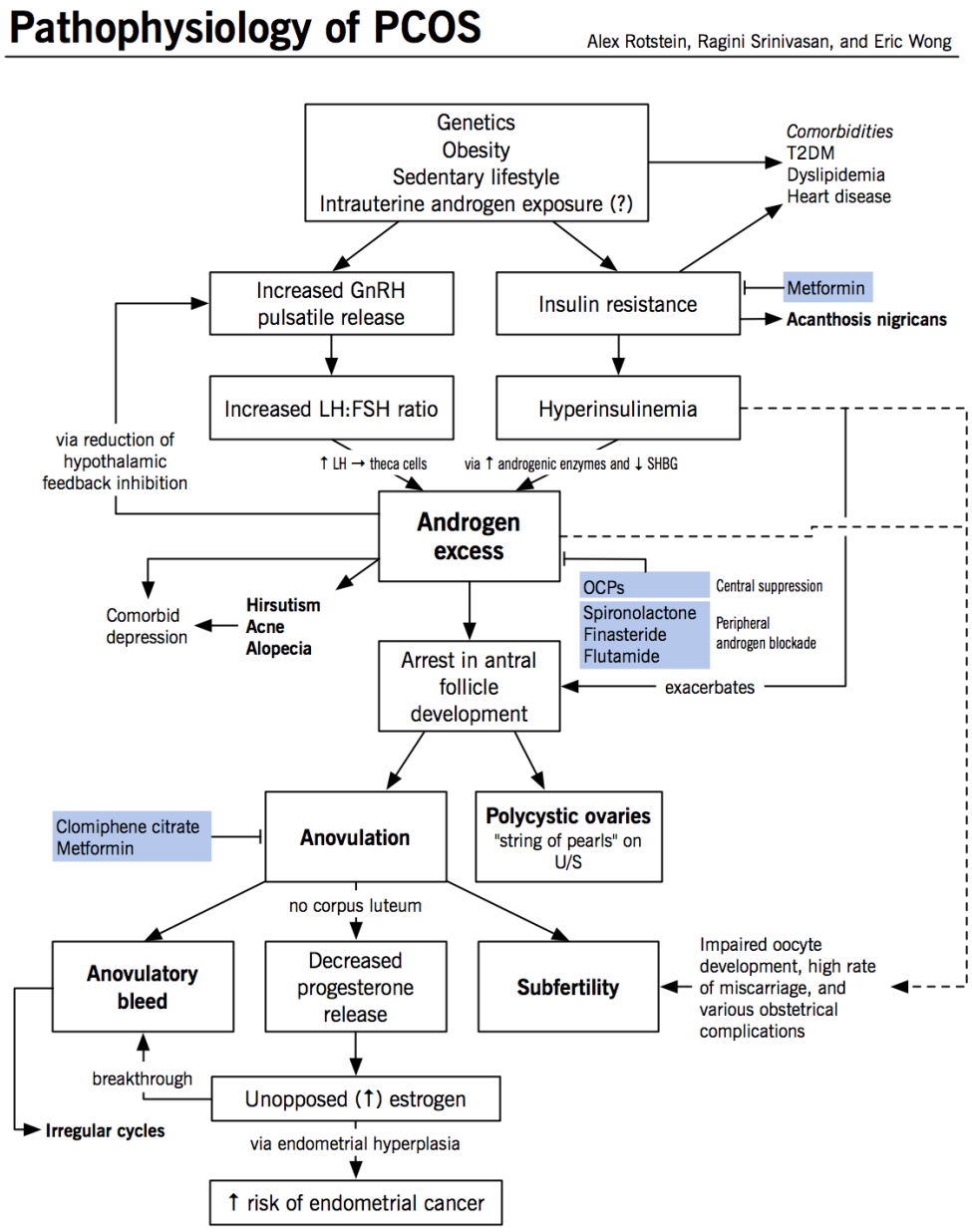
2. Genes of DM discovered:

As seen above, some people may be genetically susceptible to Non-insulindependent (NIDDM) or adult onset diabetes. Recently researchers have discovered 2 (two) genes, called MODY 1 and MODY 3, that appear to contribute to the 2 to 5 per cent of Diabetes cases that are clearly inheritable. MODY 3 gene, located on chromosome 12, produces hepatocyte nuclear factor-1α (HNF-1α), a protein found in the Liver and in the β-cells of the pancreas. Pancreatic β-cells produce insulin, the hormone that regulates blood sugar levels. "MODY 1 gene", located on chromosome 20, makes hepatocyte nuclear factor 4α (HNF 4α), a cell receptor that plays a role in HNF-1α production. The biological effects of mutant forms of HNF-1α and HNF-4α are still not known clearly.

Clinical Features and Biochemical Correlations

- Large amounts of glucose may be excreted in urine (may be 90 to 100 G/day in some cases). Loss of solute produces osmotic diuresis thus large volume of urine (polyuria).
- Loss of fluid leads to thirst and polydypsia.

- Polyphagia: Eats more frequently. More fond of sweets. The above symptoms may persist for many months in maturity-onset diabetes. In juvenile onset type-1, further symptoms develop if treatment is not started.
- Tissues including muscles received liberal supply of glucose but cannot use glucose due to absolute or relative deficiency of insulin/ or transport defect to cells. This causes weakness and tiredness.
- As glucose cannot be used for fuel, fat is mobilised leading to increase FFA- in blood and liver.
- Increased acetyl-CoA is diverted for cholesterol synthesis—
- Hypercholesterolaemia and atherosclerosis.
- Xanthomas may develop.
- Increased ketone bodies leads to acidosis, which leads to hyperventilation (“air-hunger”).
- If ketosis is severe, acetone will be breathed out, giving characteristic “fruity” smell in breath (due to acetone).
- Alongwith above, there may be excessive breakdown of tissue proteins. Deaminated amino acids are catabolised to provide energy, which accounts for loss of weight.
- Due to ketosis, develops anorexia, nausea, and vomiting.
- Continued loss of water and electrolytes increases dehydration.
- Ketoacidosis produces increasing drowsiness, leading to diabetic coma in untreated cases.



The ovaries are part of the female reproductive system. They're located in the lower abdomen on both sides of the uterus. Women have two ovaries that produce eggs as well as the hormones estrogen and progesterone. Sometimes, a fluid-filled sac called a cyst will develop on one of the ovaries. Many women will develop at least one cyst during their lifetime. In most

cases, cysts are painless and cause no symptoms.

There are various types of ovarian cysts, such as dermoid cysts and endometrioma cysts. However, functional cysts are the most common type. The two types of functional cysts include follicle and corpus luteum cysts.

Follicle cyst

During a woman's menstrual cycle, an egg grows in a sac called a follicle. This sac is located inside the ovaries. In most cases, this follicle or sac breaks open and releases an egg. But if the follicle doesn't break open, the fluid inside the follicle can form a cyst on the ovary.

Corpus luteum cysts

Follicle sacs typically dissolve after releasing an egg. But if the sac doesn't dissolve and the opening of the follicle seals, additional fluid can develop inside the sac, and this accumulation of fluid causes a corpus luteum cyst.

Symptoms of an ovarian cyst

Often times, ovarian cysts do not cause any symptoms. However, symptoms can appear as the cyst grows. Symptoms may include:

- abdominal bloating or swelling
- painful bowel movements
- pelvic pain before or during the menstrual cycle
- painful intercourse
- pain in the lower back or thighs
- breast tenderness
- nausea and vomiting

Hyperandrogenism

Hyperandrogenism is the most characteristic feature of PCOS, and some argue that it is the defining feature of the disease. Hyperandrogenism is exacerbated by hyperinsulinemia and antral follicle arrest and may itself increase the risk of follicle arrest Similar ovarian characteristics have been noted in women with other conditions of androgen excess such as

congenital adrenal hyperplasia.

Neuroendocrine abnormalities

Women with PCOS have an increase in the frequency of GnRH pulses; shorter pulses preferentially promote the production of luteinizing hormone (LH) and result in a decrease in the production of follicle stimulating hormone (FSH). Patients with PCOS often exhibit an increase in the LH:FSH ratio, which may contribute to the ovarian excess of androgens relative to estrogens. It is unclear if patients with PCOS have an intrinsically faster GnRH pulsation mechanism which initiates hyperandrogenism in the ovaries, or if oligoanovulation itself promotes more rapid pulsations in GnRH via a reduction in circulating progesterone Normally, progesterone is released from the corpus luteum following ovulation Progesterone acts to slow GnRH pulsation In PCOS, a decrease in ovulatory events may cause a decrease in circulating progesterone. Exposure to androgens in utero or prepubertally may decrease the inhibitory effects of estrogen and progesterone on the hypothalamus and contribute to increased pulsatility.

Polycystic ovaries

Polycystic ovaries are present in 20-30% of women and are not essential for the diagnosis of PCOS. The “cysts” in polycystic ovaries are not true cysts, but rather antral follicles which have arrested in development. This is thought to occur because of hormonal abnormalities:

Hyperandrogenism: arrest occurs when the granulosa cells of the ovaries normally begin to produce estrogen by aromatizing androstenedione produced by the theca cells; excess 5a-reduced androgens in the ovaries are thought to inhibit the action of aromatase and therefore reduce estradiol synthesis, which is required for further maturation

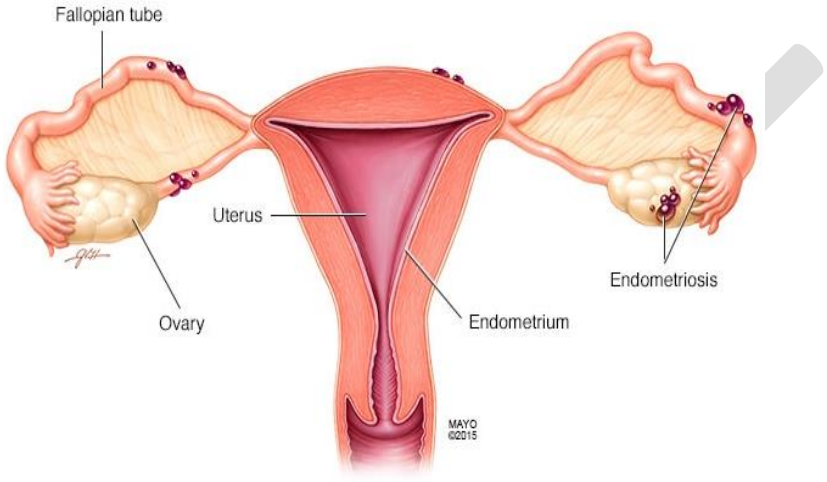
Hyperinsulinemia: exacerbates ovarian hyperandrogenism by (1) increasing 17a-hydroxylase activity in theca cells and promoting androstenedione and testosterone production; (2) promoting LH- and IGF1-stimulated androgen production; and (3) elevating free testosterone by decreasing the production of sex hormone binding globulin (SHBG).

Endometriosis

Endometriosis is an often painful disorder in which tissue that normally lines the inside of your uterus the endometrium grows outside your uterus. Endometriosis most commonly

involves your ovaries, fallopian tubes and the tissue lining your pelvis. Rarely, endometrial tissue may spread beyond pelvic organs.

With endometriosis, displaced endometrial tissue continues to act as it normally would it thickens, breaks down and bleeds with each menstrual cycle. Because this displaced tissue has no way to exit your body, it becomes trapped. When endometriosis involves the ovaries, cysts called endometriomas may form. Surrounding tissue can become irritated, eventually developing scar tissue and adhesions abnormal bands of fibrous tissue that can cause pelvic tissues and organs to stick to each other.



Symptoms

The primary symptom of endometriosis is pelvic pain, often associated with your menstrual period. Although many women experience cramping during their menstrual period, women with endometriosis typically describe menstrual pain that's far worse than usual. They also tend to report that the pain increases over time.

Common signs and symptoms of endometriosis may include:

Painful periods (dysmenorrhea). Pelvic pain and cramping may begin before period and extend several days into period.

- Pain with intercourse. Pain during or after sex is common with endometriosis.
- Pain with bowel movements or urination.

- Excessive bleeding. Occasional heavy periods (menorrhagia) or bleeding between periods (menometrorrhagia).
- Infertility. Endometriosis is first diagnosed in some women who are seeking treatment for infertility.
- Other symptoms. You may also experience fatigue, diarrhea, constipation, bloating or nausea, especially during menstrual periods.

Risk factors

Several factors place you at greater risk of developing endometriosis, such as:

- Never giving birth
- Starting period at an early age
- Going through menopause at an older age
- Short menstrual cycles — for instance, less than 27 days
- Having higher levels of estrogen in body or a greater lifetime exposure to estrogen body produces
- Low body mass index
- Alcohol consumption
- One or more relatives (mother, aunt or sister) with endometriosis
- Uterine abnormalities

Hypogonadism

Male hypogonadism is a condition in which the body doesn't produce enough testosterone the hormone that plays a key role in masculine growth and development during puberty — or has an impaired ability to produce sperm or both.

Symptoms

Hypogonadism can begin during fetal development, before puberty or during adulthood. Signs and symptoms depend on when the condition develops.

Fetal development

If the body doesn't produce enough testosterone during fetal development, the result may

be impaired growth of the external sex organs. Depending on when hypogonadism develops and how much testosterone is present, a child who is genetically male may be born with:

- Female genitals
- Ambiguous genitals — genitals that are neither clearly male nor clearly female
- Underdeveloped male genitals.

Puberty

Male hypogonadism may delay puberty or cause incomplete or lack of normal development. It can cause:

- Decreased development of muscle mass
- Lack of deepening of the voice
- Impaired growth of body hair
- Impaired growth of the penis and testicles
- Excessive growth of the arms and legs in relation to the trunk of the body
- Development of breast tissue (gynecomastia)

Causes:

Male hypogonadism means the testicles don't produce enough of the male sex hormone testosterone. There are two basic types of hypogonadism:

Primary. This type of hypogonadism also known as primary testicular failure — originates from a problem in the testicles.

Secondary: This type of hypogonadism indicates a problem in the hypothalamus or the pituitary gland parts of the brain that signal the testicles to produce testosterone. The hypothalamus produces gonadotropin-releasing hormone, which signals the pituitary gland to make follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Luteinizing hormone then signals the testes to produce testosterone.

Primary hypogonadism

Common causes of primary hypogonadism include:

Klinefelter syndrome:

This condition results from a congenital abnormality of the sex chromosomes, X and Y.

A male normally has one X and one Y chromosome. In Klinefelter syndrome, two or more X chromosomes are present in addition to one Y chromosome. The Y chromosome contains the genetic material that determines the sex of a child and related development. The extra X chromosome that occurs in Klinefelter syndrome causes abnormal development of the testicles, which in turn results in underproduction of testosterone.

Undescended testicles:

Before birth, the testicles develop inside the abdomen and normally move down into their permanent place in the scrotum. Sometimes one or both of the testicles may not be descended at birth. This condition often corrects itself within the first few years of life without treatment. If not corrected in early childhood, it may lead to malfunction of the testicles and reduced production of testosterone.

Mumps orchitis:

If a mumps infection involving the testicles in addition to the salivary glands (mumps orchitis) occurs during adolescence or adulthood, long-term testicular damage may occur. This may affect normal testicular function and testosterone production.

Hemochromatosis:

Too much iron in the blood can cause testicular failure or pituitary gland dysfunction, affecting testosterone production.

Injury to the testicles:

Because they're situated outside the abdomen, the testicles are prone to injury. Damage to normally developed testicles can cause hypogonadism. Damage to one testicle may not impair total testosterone production.

Secondary hypogonadism

In secondary hypogonadism, the testicles are normal but function improperly due to a problem with the pituitary or hypothalamus. A number of conditions can cause secondary hypogonadism, including:

Kallmann syndrome:

Abnormal development of the hypothalamus — the area of the brain that controls the

secretion of pituitary hormones — can cause hypogonadism. This abnormality is also associated with impaired development of the ability to smell (anosmia) and red-green color blindness.

Pituitary disorders:

An abnormality in the pituitary gland can impair the release of hormones from the pituitary gland to the testicles, affecting normal testosterone production. A pituitary tumor or other type of brain tumor located near the pituitary gland may cause testosterone or other hormone deficiencies. Also, the treatment for a brain tumor, such as surgery or radiation therapy, may impair pituitary function and cause hypogonadism.

Risk factors

Risk factors for hypogonadism include:

- Kallmann syndrome
- Undescended testicles as an infant
- Mumps infection affecting your testicles
- Injury to your testicles
- Testicular or pituitary tumors
- HIV/AIDS
- Klinefelter syndrome
- Hemochromatosis
- Previous chemotherapy or radiation therapy
- Untreated sleep apnea.

Cryptorchidis

The word "cryptorchidism" comes from the Greek words "kryptos," meaning "hidden," and "orchis" which means "testicle." The scrotum is a small pouch, or sac, of skin that hangs behind the penis. Inside the scrotum is a pair of testicles, the oval-shaped sex organs that form part of the male reproductive system. The testicles produce sperm and testosterone, a hormone that plays a key role in male sexual development. During gestation, the testicles form in the abdomen and gradually descend into the scrotum around the 8th month. In cryptorchidism, the testicles do not descend or do not appear.

Symptoms

Undescended testicles may be palpable or unpalpable.

A palpable, undescended testicle can be felt during a physical examination. The testicle is usually located at the end of the inguinal canal, a channel that carries the spermatic cord towards the penis and scrotum in males.

There are three main types of unpalpable undescended testicle:

- Abdominal: the least common location for an undescended testicle is in the abdomen
- Inguinal: The testicle has moved into the inguinal canal, but has not moved far enough down to be detected by touch
- Atrophic or absent: The testicle is either very small, or it has never formed.

An unpalpable undescended testicle cannot be felt during a physical examination.

Risk factors

The following risk factors are linked to cryptorchidism:

- Premature birth, and the earlier the birth,
- the higher the risk Infants whose birth weight is below 5.5 lb have double or triple the risk
- Down syndrome and other conditions that can slow fetal growth
- Exposure to pesticides or hormone-disrupting chemicals, like DES
- Family history of problems of genital development
- Tobacco consumption during pregnancy by the mother.
- Consuming more than five alcoholic drinks a week during pregnancy has also been linked to temporary cryptorchidism.

Causes

In the early stages, all fetuses have identical reproductive precursors, regardless of sex. In other words, they have structures that can develop into either male or female reproductive organs. The child receives a pair of sex chromosomes from its mother and father. Sex chromosomes are a pair of DNA molecules. The chromosomes will be XX if the fetus is female and XY if male. As the fetus develops, the XY gene promotes the development of the testis. The

testes produce hormones that then promote the growth of the male reproductive tract, and these prevent female development from occurring.

It is thought that the problems of absent or undeveloped testicles happen at this stage. Abnormal genital development may also stem from androgen insensitivity syndrome, a genetic disorder in which XY fetuses do not respond to male hormones, or androgens, such as testosterone.

In this case, the infant is born looking like a girl, with a short, blind, pouch vagina but with no uterus, ovaries, or fallopian tubes. The testes are present in the abdomen or the inguinal canal. In most cases of undescended testicle, a combination of genetics, maternal health, and some environmental factors are thought to disrupt the hormones, physical changes, and nerve activity that is involved in the development of the testicles.

Diagnosis

These may include:

- ✓ Ultrasound scan to locate the testicle, if it is in the groin
- ✓ MRI scan with a contrast agent that is injected into the bloodstream, to show whether the testicle is in the groin or abdomen
- ✓ Laparoscopy involves a tube with a tiny video camera that is inserted through a small incision in the abdomen. Corrective surgery may be possible during this procedure
- ✓ Open surgery may be necessary in rare, complicated cases, to explore directly inside the abdomen.

Treatment

In around half of all patients with cryptorchidism, the testicle will descend on its own within 3 months. However, in 1 to 2 of every 100 cases it does not descend by the time a child is 6 months old, and surgery is needed.

Orchidopexy

Orchidopexy or orchiopexy is a surgical procedure that is commonly used to free an undescended testicle and implant it into the scrotum.

It is usually done between the ages of 6 to 18 months. It should definitively be performed before a child is two years old, as delaying the operation may increase the long-term risk of developing testicular cancer or infertility.

The testicles reside in the scrotum, because they need to be at a lower temperature than the rest of the body to produce sperm; if they are not at this temperature, it will impair sperm production.

The surgeon makes a small incision in the abdomen and uses small surgical instruments to move the testicle down the inguinal canal and place it in the scrotum, using a second incision. The inguinal canal is normally sealed to stop the testicle from going back up.

Testicular carcinoma

Testicular cancer is a disease in which malignant (cancer) cells form in the tissues of one or both testicles. The testicles are 2 egg-shaped glands located inside the scrotum (a sac of loose skin that lies directly below the penis). The testicles are held within the scrotum by the spermatic cord, which also contains the vas deferens and vessels and nerves of the testicles.

The testicles are the male sex glands and produce testosterone and sperm. Germ cells within the testicles produce immature sperm that travel through a network of tubules (tiny tubes) and larger tubes into the epididymis (a long coiled tube next to the testicles) where the sperm mature and are stored.

Almost all testicular cancers start in the germ cells. The two main types of testicular germ cell tumors are seminomas and nonseminomas. These 2 types grow and spread differently and are treated differently. Nonseminomas tend to grow and spread more quickly than seminomas. Seminomas are more sensitive to radiation. A testicular tumor that contains both seminoma and nonseminoma cells is treated as a nonseminoma.

Testicular Cancer Symptoms & Signs

The first and early sign of testicular cancer is most commonly a little ("pea-sized") lump on the testis (painless testicular lump). There may be no real pain, at most just a dull ache in the

lower abdomen or groin, perhaps a sensation of dragging and heaviness. The signs and symptoms of cancer of the testicle may include:

- a lump in or on a testicle (testicular lump) is the most common sign;
- any enlargement or swelling of a testicle and/or scrotum;
- shrinking of a testicle;
- a feeling of heaviness in the scrotum (scrotal heaviness);
- a dull ache in the lower abdomen (lower abdominal pain) or in the groin.

Symptoms of testicular cancer may include:

- A painless lump or swelling on either testicle. If found early, a testicular tumor may be about the size of a pea or a marble, but it can grow much larger.
- Pain, discomfort, or numbness, with or without swelling, in a testicle or the scrotum.
- Change in the way a testicle feels or a feeling of heaviness in the scrotum. For example, 1 testicle may become firmer than the other testicle. Or testicular cancer may cause the testicle to grow bigger or to become smaller.
- Dull ache in the lower abdomen or groin
- Sudden buildup of fluid in the scrotum
- Breast tenderness or growth. Although rare, some testicular tumors make hormones that cause breast tenderness or growth of breast tissue, a condition called gynecomastia.
- Lower back pain, shortness of breath, chest pain, and bloody sputum or phlegm can be symptoms of later-stage testicular cancer.
- Swelling of 1 or both legs or shortness of breath from a blood clot can be symptoms of testicular cancer. A blood clot in a large vein is called deep venous thrombosis or DVT. A blood clot in an artery in the lung is called a pulmonary embolism and causes shortness of breath. For some young or middle-aged men, developing a blood clot may be the first sign of testicular cancer.

Question	A	B	C	D	Answer
In hyperparathyroidism, which of the following is correct?	Low serum calcium	High serum phosphorus	Low serum calcium and high serum phosphorus	High serum calcium and low serum phosphorus	**High serum calcium and low serum phosphorus**
The hypothalamus controls the anterior pituitary by means of	releasing hormones	second messengers	third messengers	antibodies	**releasing hormones**
Oxytocin and ADH are produced by the _____ and stored in the _____.	hypothalamus; neurohypophysis	adenohypophysis; kidneys	anterior pituitary; thyroid	adrenal cortex; adrenal medulla	**hypothalamus; neurohypophysis**
If a person drinks a large amount of water in a short period of time, he or she may die from water toxicity. ADH can help prevent water retention through interaction with target cells in the	anterior pituitary	posterior pituitary	adrenal gland	kidney	**kidney**
Which of the following statements about the hypothalamus is incorrect?	It functions as an endocrine gland.	It is part of the central nervous system.	It is subject to feedback inhibition by certain hormones.	It secretes tropic hormones that act directly on the gonads.	**It secretes tropic hormones that act directly on the gonads.**
Which hormone exerts antagonistic action to PTH (parathyroid hormone)?	Thyroxine	epinephrine	growth hormone	calcitonin	**calcitonin**
Which of the following glands shows both endocrine and exocrine activity?	Pituitary	Parathyroid	Salivary	Pancreas	**Pancreas**
What happens when beta cells of the pancreas release insulin into the blood?	Blood glucose levels rise to a set point and stimulate glucagon release.	Body cells take up more glucose.	The liver breaks down glycogen to glucose.	Alpha cells are stimulated to release glucose into the blood.	**Body cells take up more glucose.**
Which of the following hormones is (are) secreted by the adrenal gland in response to stress and promote(s) the synthesis of glucose from noncarbohdyrate substrates?	glucagon	glucocorticoids	epinephrine	thyroxine	**glucocorticoids**
Which of the following is secreted by the pancreas?	ecdysone	glucagon	thyroxine	oxytocin	**glucagon**
Which of the following is the most likely explanation for hypothyroidism in a patient whose iodine level is normal?	a disproportionate production of T3 to T4	hyposecretion of TSH	hypersecretion of TSH	hypersecretion of MSH	**hyposecretion of TSH**
Which of the following can cause myxedema coma?	Advanced progression of hypothyroidism	End-stage Graves' disease	Overdose of propylthiouracil	Uncontrolled diabetes	**Advanced progression of hypothyroidism**
Which of the following is the most common cause of hypothyroidism?	Acute thyroiditis	Hashimoto's disease	Radioactive iodine exposure	Thyroidectomy	**Hashimoto's disease**
Which of the following is the most common cause of goiter?	Iodine deficiency	Iodine excess	Kwashiorkor	Marasmus	**Iodine deficiency**
Diabetes insipidus results from	hyposecretion of insulin	hypersecretion of insulin	hyposecretion of aldosterone	hypersecretion of ADH	**hyposecretion of insulin**
Long-term therapy with steroid drugs, such as cortsone, can cause osteoporosis and muscle wasting because of	increased blood glucose	increased protein breakdown	bacterial breakdown of bone and muscle	increased protein build up	**increased protein breakdown**
Which of the following confirmed values meet the diagnostic threshold for diabetes?	fasting blood glucose ≥ 140 mg/dl	random glucose > 160 mg/dl	2 hour post prandial glucose ≥ to 126 mg/dl	fasting blood glucose ≥ 126 mg/dl	**fasting blood glucose ≥ 140 mg/dl**
Which of the following statements is correct?	Insulin suppresses the activity of glycogen synthase	Insulin mediates glucose uptake in the brain	"Prediabetes" is a condition characterized by an increased risk for the future development of type 2 diabetes	The rise in insulin concentration after meal ingestion is reduced in type 1 but not in type 2 diabetes	**"Prediabetes" is a condition characterized by an increased risk for the future development of type 2 diabetes**
Insulin deficiency is associated with	Reduced lipolysis	Increased ketogenesis	Reduced gluconeogenesis	Reduced proteolysis	**Increased ketogenesis**
The risk factors for type 2 diabetes mellitus include:	family history	being overweight	high intake of dietary fat	All of the options listed are correct	**All of the options listed are correct**
The pathogenesis of hyperglycemia in type 2 diabetes includes all the following mechanisms except for:	Increased glucose production by the liver	Impaired insulin secretion	Decreased glucose uptake from the skeletal muscle	All of the options given are correct	**All of the options given are correct**
Calcitonin is synthesized in	parathyroid glands	Thyroid gland	pars intermediary of pituitary	Adrenal cortex	**Thyroid gland**
The number of aminoacid in calcitonin	9	51	32	84	**32**
parathyroid hormone is synthesized in	Chief cells of Parathyroid glands	Oxyphil cells of parathyroid glands	Para follicular cells of thyroid glands	Follicular cells of thyroid gland	**Chief cells of Parathyroid glands**
Half – life of parathyroid hormone is	A few years	A few seconds	A few hours	A few days	**A few seconds**
All the following may occur in hyperthyroidism except	Goitre	Increased appetite	loss of weight	Low BMR	**Low BMR**
α – cells of Islets of langerhans secrete	Insulin	Glucagon	Somatostatin	Cholecystokinin	**Glucagon**
Insulin is secreted by following cells of Islets of langerhans	α cells	β cells	δ cells	F cells	**β cells**
Insulin is required for the active uptake of glucose by most of the cell except	Muscle cells	Renal tubular cells	Adipocytes	liver cells	**liver cells**
Insulin decreases	Glycogenesis	Glucolysis	Glyconeogenesis	Tubular reabsorption of glucose	**Glyconeogenesis**
Insulin increases	Glycogenesis	Gluconeogenesis	Lipolysis	Blood sugar	**Glycogenesis**
Zona glomerulosa of adrenal cortex synthesis	Glucocorticoids	Mineralocorticoids	Androgen	Estrogen and progesterone	**Mineralocorticoids**
Cortisol is a	Glucocorticoid	Mineralocorticoid	Androgen	Estrogen	**Glucocorticoid**
A woman with polycystic ovary syndrome (PCOS) may have these symptoms:	hirsutism (excessive body and facial hair)	ovarian cysts	irregular menses	all of the above	**all of the above**
What is osteoporosis?	A disorder characterized by impaired growth of dwarfism	A disorder characterized by apparent lack of aging	A disorder characterized by the growth of cysts on the ovaries which manifests in excess weight, hirsuitism and mood disorders	A disorder in which bones become fragile and easily breakable. It can result from abnormally low levels of estrogen or testosterone	**A disorder in which bones become fragile and easily breakable. It can result from abnormally low levels of estrogen or testosterone**
Thyroid disorders can result in which of the following?	Hirsuitism and PCOS	Fragile bones and recurrent injuries	Deficits in autoimmunity and weight fluctuations	Deficits in growth and gender identity	**Deficits in autoimmunity and weight fluctuations**
What are the female gonads?	Breasts	Testes	Pituitary glands	Ovaries	**Ovaries**
Used to treat primary hypogonadism:	conjugated estrogen	ethinyl estradiol	both	neither	**both**
Amenorrhea	is the age at the first menstrual flow.	may result from obesity	may occur in women who are very lean and physically active.	is an excessively heavy menstrual flow	**may occur in women who are very lean and physically active.**
Gonadotropoin releasing hormone is a	sex steroid.	hypothalamic hormone.	gonadotropin.	androgen.	**hypothalamic hormone.**
If the developing testes are functioning normally and producing testosterone, yet the embryonic target tissues lack receptors for responding to this hormone, a fetus would develop	ovaries.	normal male external genitalia.	Klinefelter's syndrome.	testicular feminization syndrome.	**testicular feminization syndrome.**
The function of the enzyme 5a-reductase is to	convert testosterone into the active hormone, dihydrotestosterone.	cause the fetal gonad to develop into a testis.	suppress development of Müllerian duct derivatives.	convert testosterone in the brain to estradiol-17ß.	**convert testosterone into the active hormone, dihydrotestosterone.**
The male sex hormones are called:	Allogens.	Androgens.	Oestrogens.	Spermatocytes	**Androgens.**
Most testicular cancers are:	Congenital.	Germ cells tumours.	As a result of trauma.	Melanomas	**Germ cells tumours.**
_____ is one of the most common symptoms of endometriosis.	Bloating	Infertility	Pelvic muscle spasms	Diarrhea	**Infertility**
Undifferentiated spermatogenic cells are called	spermatogonia.	primary spermatocytes.	secondary spermatocytes.	spermatids	**spermatogonia.**
Seminal vesicles produce	sperm cells.	testosterone.	fructose-rich fluid.	estrogen.	**fructose-rich fluid.**
The seminal vesicles are located	inferior to the prostate within the urogenital diaphragm.	within the lobules of the testes.	within the spermatic cord.	posterior and inferior to the urinary bladder, in front of the rectum	**posterior and inferior to the urinary bladder, in front of the rectum**
Testosterone is produced by	spermatozoa.	sustentacular cells.		the hypothalamus.	**interstitial cells**
A function of FSH in the male is to	inhibit progesterone.	initiate testosterone production.	increase protein synthesis.	initiate spermatogenesis	**initiate spermatogenesis**
An abnormal human male phenotype involving an extra X-chromosome (XXY) is a case of	Edward's syndrome	Klinefelter's syndrome	intersex	Down's syndrome	**Klinefelter's syndrome**
Drug effectively used in treatment of Cushing's syndrome is:	Insulin	Prednisolone	Ketoconazole	High dose multivitamin	**Ketoconazole**
Addison's disease is associated with serum levels of	Elevated potassium and low sodium	Elevated Sodium and low potassium	Elevated sodium and potassium	Decreased sodium and potassium	**Elevated potassium and low sodium**
Calcitonin is _____	regulates the calcium level in blood	is balanced by the action of parathyroid hormone	increases the deposit of calcium in bone	all of the above	**all of the above**
Parathyroid hormone (PTH) _____.	stops the absorption of calcium from the intestine	stimulates the release of calcium by the kidneys	causes blood calcium level to decrease	causes blood phosphate level to decrease	**causes blood phosphate level to decrease**
A person with Addison disease _____	is unable to replenish blood glucose levels under stressful conditions	develops dramatically more male features	develops a rounded face and edema	has overgrowth of hands and face	**is unable to replenish blood glucose levels under stressful conditions**
The pancreatic islets produce _____.	insulin and glucagon	pancreatin	ACTH and aldosterone	pancreatic digestive enzymes	**insulin and glucagon**
Insulin functions to _____	promote the storage of nutrients	lower the blood glucose level by stimulating liver, fat and muscle cells to metabolize glucose	stimulate uptake of glucose by cells	all of the above	**stimulate uptake of glucose by cells**
Adrenal cortex does not produce:	Glucocorticoid hormone	Adreno corticotropic hormone	Androgen	Aldosterone	**Adreno corticotropic hormone**
Thyroid gland takes up circulating iodine	By simple diffusion	By facilitated diffusion	By active uptake	In exchange for chloride	**By active uptake**