



# Review : AIIMS

## MD/MS Entrance Exam

## November 2010

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**Anatomy**

**1. True about scalenus anterior is :**

a. Inserted on sclanae tubercle on 2nd rib
b. Anterior to trverse cervical artery
c. Separates subclavian artery and vein
d. Pierced by phrenic nerve

**: C Separates subclavian artery and vein**

- Inserted on sclanae tubercle on **1st rib**
- **Posterior** to trverse cervical artery
- Separates subclavian artery (posteriorly) and vein (anteriorly)
- **Posterior** to phrenic nerve

2. **All are supplied by Superior gluteal nerve except : (Repeat)**

a. Gluteus maximus
b. Gluteus minimus
c. Gluteus medius
d. Tensor fascia lata

**: A Gluteus maximus**

| | |
|---|---|
| **Superior gluteal nerve** (L4,5 & S1) &a. | **Gluteus medius**<br>**Gluteus minimus**<br>**Tensor Fascia lata** |
| Inferior gluteal nerve (L5 , S1 &2) & a. | Gluteus Maximus |

**3. Lacrimation is lost in lesion of : (repeat)**

a. Nasociliary n.
b. Greater petrosal n.
c. Anterior ethemoidal n.
d. Superior orbital n.

**: B Greater petrosal n.**

Lacrimal Gland
Blood supply : lacrimal a. (ophthalmic a.)
Nerve supply : Lacrimal n. (sensory + secretomotor)
Secretomotor fibers :
Lacrimatory nucleus→ nervus intermedius → geniculate ganglion of fascial nerve → **Greater Petrosal nerve** → nerve of pterygoid canal → pterygopalatine ganglion → zygomatic nerve → zygomatico temporal nerve → lacrimal nerve

**4. Derivatives of septum trversum are all except :**

a. Falciform ligament
b. Coronary ligament
c. Ligamentum teres hepatis
d. Lesser omentum

**: C** Ligamentum teres hepatis

Stomach :
Dorsal border is attached to posterior abdominal wall by dorsal mesogastrium :
Derivatives of dorsal mesogastrium –

- Greater omentum
- Linorenal ligament
- Gastrophrenic ligament
- Gastrosplenic ligament

Ventral border is *attached to septum trversum by ventral mesogastrium*
Liver & diaphragm are formed in substance of septum trversum
Derivatives of **ventral mesogastrium** :

- **Lesser omentum** (part between stomach & liver)
- **Coronary** ligament & **Falciform** ligament (stomach & diaphragm /ant abd wall)
- **Triangular** ligaments

**5. All of the following develop from mesentery of stomach except :**
a. Liver
b. Spleen
c. Kidney
d. Pancreas

**C kidney**

**6. All of the following are parts of lower genital tract sphincter in females except : (Repeat)**
a. External urethral sphincter
b. Internal urethral sphincter
c. Bulbospongiosus
d. Pubovaginalis

**B. internal urethral sphincter**

Sphincter urethra = External urethral sphincter (action is similar to bulbospongiosus in ejaculating last drop of urine)
- Superficial fibers
- Deep circular fibers

Deep treverse perinei

Both are supplied by perineal branch of pudendal nerve

**7. Neonate is able to breath & suck (swallow) at the same time due to :**
a. Wide short tongue
b. Short soft palate
c. High larynx
d. Short pharynx

**C. high larynx**

At birth larynx is high in position → placing epiglottis in close contact with soft palate → allows infant to breathe through nose while sucking and swallowing

**8. Tensor tympani is supplied by :**
a. Trigeminal nerve
b. Facial nerve
c. Glossopharyngeal nerve
d. Vagus nerve

**A. Trigeminal nerve**

Muscles of middle ear :

| | | |
|---|---|---|
| Tensor tympani | 1st branchial arch | Mandibular nerve (Trigeminal nerve) |
| Stapedius | 2nd branchial arch | Facial nerve |

**9. Structure to reach adult size before birth :**
a. Mastoid process
b. Maxilla
c. Ossicles of ear
d. Parietal bone

**C. Ossicles of Ear**

1st bones to ossify in body
Time : 4th month of intrauterine life

| | |
|---|---|
| Dorsal end of meckles cartilage of 1st pharyngeal arch | Malleus Incus |
| Dorsal end of cartilage of 2nd pharyngeal arch | Stapes |

**10. Most sensitive investigation for DCIS breast**
a. Mammography
b. USG
c. MRI

**Mammography**

HR-MRI (not plain MRI) > Mammography
Mammography is a screening test (highly sensitive)

d. PET

Features suggestive of Breast cancer on mammogram:
- Microcalcification
- Mass effect
- Architectural distortion
- Skin thickening
- Ductal dilatation
- Asymmetry of breast
- Fibro nodular densities

**11. Condition responsible for cecum found below stomach :**
a. Malrotation
b. Nonrotation
c. Reverse rotation
d. Mixed rotation

Malrotation or **Nonrotation**

## Physiology

**12. True regarding cyanosis is :**
a. Early feature of hypoxia
b. Late feature of hypoxia
c. Absence of cyanosis indicates good tissue oxygenation
d. Absence of cyanosis indicates adequate airway

**late feature of hypoxia**

Cyanosis = blue colored skin or mucus membrane when deoxygenated Hb >5gm %

Hb has Sigmoidal ODC = Hb is 97% saturated even if PaO2 falls upto 60 mm Hg
If paO2 falls below 60 mm Hg → concentration of deoxy Hb starts increasing
Hence Cyanosis is a Late (not an early) feature of Hypoxia

Absence of cyanosis doesn't mean good tissue oxygenation : Anemic hypoxia (Total Hb is less) or histotoxic or stagnant hypoxia (% saturation of Hb is normal as PaO2 is normal) → no deoxyHb to cause cyanosis But still tissues are deprived of oxygen

Absence of cyanosis doesn't always indicates adequate airway : because if inadequate airway with anemia / high % saturation of Hb will not show cyanosis

**13. Hypoxemia depends on all except :**
a. FiO2
b. Hb
c. PaCO2
d. High altitude

B. **Hb**

Hb determines only bound form of oxygen

Hypoxemia = low Partial pressure of free oxygen in blood <60 mm Hg (8 Kpa) / <90% Oxygen saturation of Hb
[it excludes decreased oxygen content by low/abnormal Hb]

$$P_{Alveolar}O2 = [\{P_{atm} - P_{water}\} \times FiO2] - (P_ACO2/_{Respi\ quotient} \times Q)$$

**14. Negative pleural pressure is maintained by :**
a. Negative alveolar pressure
b. Uniform distribution of surfactant over alveoli
c. Lymphatic drainage of pleural fluid
d. Presence of cartilage in upper airway

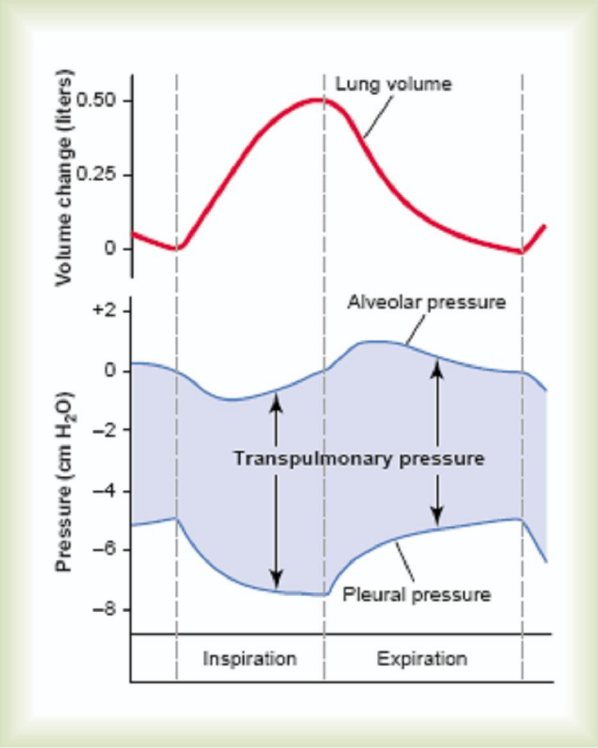
A. lymphatic drainage of pleural fluid

Surfactant is responsible for prevention of lung collapse beyond a particular point : reduce negative pleural pressure

Cartilage maintain upper airway : no relation to pleural pressure

Negative intra pleural pressure is due to opposite elastic movement of lung & chest wall : when lung tries to collapse – chest wall move out to prevent that

*Pleural pressure* is the pressure of the fluid in the thin space between the lung pleura and the chest wall pleura : this is normally a slight suction, which means a slightly *negative* pressure. The normal pleural pressure at the beginning of inspiration is about –5 centimeters of water, which is the amount of suction required to hold the lungs open to their resting level. Then, during normal inspiration, expansion of the chest cage pulls outward on the lungs with greater force and creates more negative pressure, to an average of about –7.5 centimeters of water. Then, during expiration, the events are essentially reversed.




**"Negative Pressure" in Pleural Fluid.** A negative force is always required on the outside of the lungs to keep the lungs expanded. This is provided by **negative pressure in the normal pleural space.The basic cause of this negative pressure is pumping of fluid from the space by the lymphatics (which is also the basis of the negative pressure found in most tissue spaces of the body)**. Because the normal collapse tendency of the lungs is about –4 mm Hg, the pleural fluid pressure must always be at least as negative as –4 mm Hg to keep the lungs expanded. Actual measurements have shown that the pressure is usually about –7 mm Hg, which is a few millimeters of mercury more negative than the collapse pressure of the lungs.Thus, the negativity of the pleural fluid keeps the normal lungs pulled against the parietal pleura of the chest cavity, except for an extremely thin layer of mucoid fluid that acts as a lubricant.

**15. All are absorbed in PCT except :**
a. Bicarbonate
b. Phosphate
c. Glucose
d. H+

**H+**

**16. All of the following affect resting ventilation except :**
a. J receptors
b. Stretch receptors
c. PCO2
d. PO2

**J receptors**

On **normal inspiration** lung expand → stretch **recptors** (mechanoceptros) → stimulate Apneustic / pneumotaxic centre → expiration (**Hering-Breur reflex**)
: thus regulate resting respiratory rate

Resting ventilation is controlled by medullary respiratory centres – responsive to peripheral & central **chemoreceptors :** which are sensitive to **hypoxia / hypercarbia / high H+ concentration**

**J receptors** does Not regulate resting ventilation
*Juxtacapillary* receptors in alveolar *interstitium* (innervated by *Vagus*) : activated **only in pathological conditions** like
- Low oxygenation : pul edema / pul emboli / pneumonia / barotraumas
- Hyperinflated lungs
- i.v./intracardiac chemicals

stimulation to J receptors→ increasing Respiratory rate /ventilation + subjective sensation of difficult breathing (dyspnea)

*apnea → J recptors → rapid breathing + bradycardia + hypotension* : Pulmonary chemoreflex

**17. Co2 is 20 times more diffusible than O2 because of :**
a. High solubility in plasma
b. Low PCO2 in alveoli
c. Low Co2 density
d. Low CO2 molecular weight

**High solubility in plasma**

| CO2 | O2 |
|---|---|
| 1.5 times denser (1.98 kg/m3) | Less |
| High MW (12 +16 = 28 g) | Less MW |
| Low partial pressure in alvoli | More |
| 20 times soluble in plasma – 20 times more diffusible than O2 | Less |

CO2 Transport in blood :
Bicarbonate 68% > carbamino compounds 22% > free form (dissolved) 10%

**18. Diffusion capacity of lung is measured by :**

**Carbon monoxide**

a. CO2
b. Carbon monoxide
c. Nitrogen
d. Oxygen

The **oxygen diffusing capacity** can be calculated from measurements of (1) alveolar Po2, (2) Po2 in the pulmonary capillary blood, and (3) the rate of oxygen uptake by the blood.
However, measuring the Po2 in the pulmonary capillary blood is so difficult and so imprecise that it is not practical to measure oxygen diffusing capacity by such a direct procedure, except on an experimental basis.
To obviate the difficulties encountered in measuring oxygen diffusing capacity directly, physiologists usually measure **carbon monoxide diffusing capacity** instead and then calculate the oxygen diffusing capacity from this.
Principle :

- A small amount of carbon monoxide is breathed into the alveoli, and the partial pressure of the carbon monoxide in the alveoli is measured from appropriate alveolar air samples.
- The carbon monoxide pressure in the blood is essentially zero, because hemoglobin combines with this gas so rapidly that its pressure never has time to build up.
- Therefore, the pressure difference of carbon monoxide across the respiratory membrane is equal to its partial pressure in the alveolar air sample.
- Then, by measuring the volume of carbon monoxide absorbed in a short period and dividing this by the alveolar carbon monoxide partial pressure, one can determine accurately the carbon monoxide diffusing capacity.
- To convert carbon monoxide diffusing capacity to oxygen diffusing capacity, the value is multiplied by a factor of 1.23 because the diffusion coefficient for oxygen is 1.23 times that for carbon monoxide.
- Thus, the average diffusing capacity for carbon monoxide in young men at rest is 17 ml/min/mm Hg, and the diffusing capacity for oxygen is 1.23 times this, or 21 ml/min/mm Hg.

**19. All can pass through Blood brain Barrier except :**
a. Proteins
b. Gases
c. Water
d. Lipophilic substances

**Proteins**

- In general, the blood–cerebrospinal fluid and bloodbrain barriers are
- **highly permeable** to **water, carbon dioxide, oxygen,** and most **lipid-soluble substances** such as **alcohol and anesthetics**;
- **slightly permeable** to **electrolytes** such as sodium, chloride, and potassium; and
- **totally impermeable** to **plasma proteins** and most **non–lipid-soluble large organic molecules**.
  Therefore, the blood–cerebrospinal fluid and blood-brain barriers often make it impossible to achieve effective concentrations of therapeutic drugs, such as protein antibodies and non–lipid-soluble drugs, in the cerebrospinal fluid or parenchyma of the brain

**20. pacemaker for rhythmic respiration (Repeat)**

a. prebottzinger complex
b. dorsal group neurons
c. pneumotaxic centre
d. apneustic centre

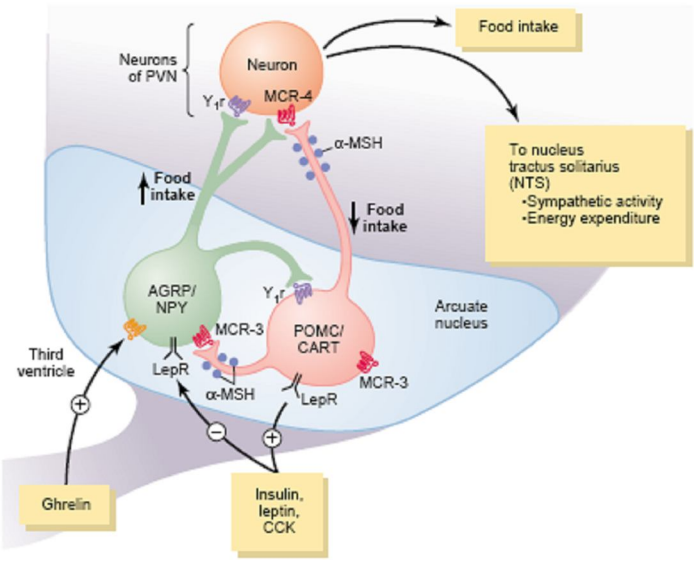
prebottzinger complex

| | |
|---|---|
| Voluntary respiration | Cerebral cortex motor area |
| Involuntary respiration | |
| Initiation of inspiration | prebottzinger complex in medulla → phrenic n. |
| Taxing b/w inspiration & expiration | Pneumotaxic centre in pons |

**21. which of the following substance secreted by stomach stimulate appetite ?**

a. orexins
b. ghrelin
c. CCK
d. Insulin like growth factor

Ghrelin




Control of energy balance by two types of neurons of the arcuate nuclei:
(1) pro-opiomelanocortin (POMC) neurons that release amelanocyte- stimulating hormone (a-MSH) and cocaine- and amphetamine-regulated transcript (CART), decreasing food intake and increasing energy expenditure; and

(2) neurons that produce agouti-related protein (AGRP) and neuropeptide Y (NPY), increasing food intake and reducing energy expenditure. a-MSH released by POMC neurons stimulates melanocortin receptors (MCR-3 and MCR-4) in the paraventricular nuclei (PVN), which then activate neuronal pathways that project to the nucleus tractus solitarius (NTS) and increase sympathetic activity and energy expenditure.

- AGRP acts as an antagonist of MCR-4.
- Insulin, leptin, and cholecystokinin (CCK) are hormones that inhibit AGRP-NPY neurons and stimulate adjacent POMC-CART neurons, thereby reducing food intake.
- Ghrelin, a hormone secreted from the stomach, activates AGRP-NPY neurons and stimulates food intake.

Arcuate nuclei of hypothalamus has 2 types of neurons

| | | |
|---|---|---|
| *proopiomelanocortin (POMC) neurons* | produce a-MSH (act on MCR-3 & 4 receptors in paravenricular nuclei)+ cocaine- and amphetamine-related transcript (CART), | decreases food intake and increases energy expenditure |
| Neurons producing ***orexigenic substances*** | ***neuropeptide Y** (NPY) and **agouti-related protein** (AGRP).* | **increases food intake** and reduces energy expenditure |

**Decrease Feeding (Anorexigenic)**

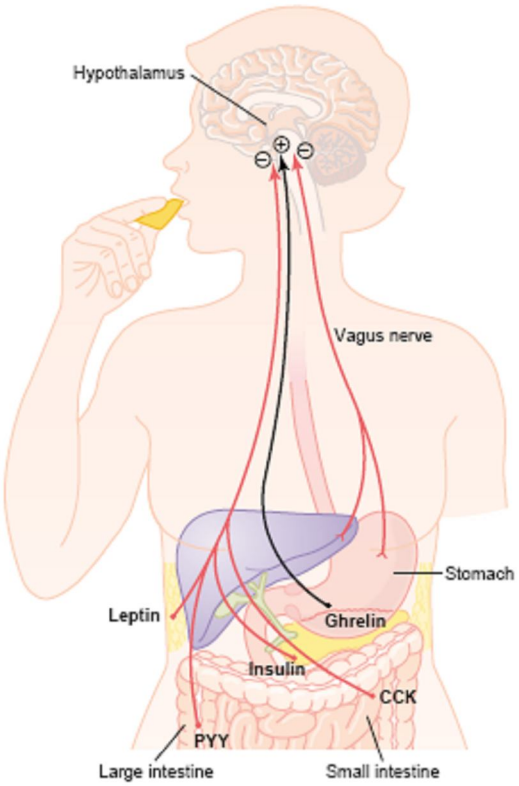
α-Melanocyte-stimulating hormone (α-MSH)
Leptin
Serotonin
Norepinephrine
Corticotropin-releasing hormone
Insulin
Cholecystokinin (CCK)
Glucagon-like peptide (GLP)
Cocaine- and amphetamine-regulated transcript (CART)
Peptide YY (PYY)

**Increase Feeding (Orexigenic)**

Neuropeptide Y (NPY)
Agouti-related protein (AGRP)
Melanin-concentrating hormone (MCH)
Orexins A and B
Endorphins
Galanin (GAL)
Amino acids (glutamate and γ-aminobutyric acid)
Cortisol
Ghrelin

**Ghrelin—a Gastrointestinal Hormone—Increases Feeding.**

- *source* the **oxyntic cells of the stomach > intestine**.
- Blood levels of ghrelin rise during fasting, peak just before eating, and then fall rapidly after a meal, suggesting a possible role in stimulating feeding.
- Also, administration of ghrelin increases food intake in experimental animals. However, its physiologic role in humans is still uncertain




- Secrete GH from anterior pituitary
- Ghrelin Receptors (GHS) : G protein coupled : in arcuate nucleus & lateral hypothalamus & vagal afferent bodies and nerve endings throughout g.i.t.
- Also plays a role in neurotrophy : in hippocampus : essential for cognitive adaptation to changing environment and process of learning

Feedback mechanisms for control of food intake.

- Stretch receptors in the stomach activate sensory afferent pathways in the vagus nerve and inhibit food intake.
- **Peptide YY (PYY), cholecystokinin (CCK),** and **insulin** are gastrointestinal hormones that are released by the ingestion of food and **suppress further feeding**.
- **Ghrelin** is released by the **stomach,** especially during fasting, and **stimulates appetite.**
- **Leptin** is a hormone produced in increasing amounts by **fat cells** as they increase in size; it **inhibits food intake**

**22. All are true about neuropeptide Y except :**

a. Consist of 36 amino acids
b. Decreased in starvation
c. Decreses thermogenesis
d. Secretion is regulated by melanocortin

**Decreased in starvation**

**Neuropeptide Y**

- Polypeptide: **36 amino acid** residues that is closely related to pancreatic polypeptide
- It is present in many parts of the brain and the autonomic nervous system

| | |
|---|---|
| autonomic nervous system : noradrenergic neurons | ▪ released by high-frequency stimulation.<br>▪ **Cotransmitter :** It augments the vasoconstrictor effects of **norepinephrine.**<br>▪ Circulating neuropeptide Y from sympathetic nerves increases with severe exercise inhumans |
| hypothalamus | mediates increased appetite and increases in food intake |

- Y1, Y2, Y4, Y5, and Y6 receptors for this polypeptide have been cloned.
- The small granulated vesicles in postganglionic noradrenergic neurons contain ATP and norepinephrine and the **large granulated vesicles** contain neuropeptide Y.
- There is evidence that low-frequency stimulation promotes release of ATP whereas **high-frequency stimulation** causes release of neuropeptideY
- acetylcholine acts presynaptically to reduce norepinephrine release from the sympathetic nerves, and conversely, neuropeptide Y released from noradrenergic endings may **inhibit the release of acetylcholine**
- Neuropeptide Y-containing neurons have their **cell bodies in the arcuate nuclei** and

- **project to the paraventricular nuclei.**
- Neuropeptide Y mRNA in the hypothalamus **increases during feeding** and **decreases during satiety.**
- Neuropeptide Y exerts its effect through three known receptors—**Y1, Y2, and Y5—all coupled to G proteins.**
- Activation of the **Y5 receptor increases food intake**, but the situation is complex because activation of the **Y2 receptor has an apparent inhibitory effect**.
- Knockout of the neuropeptide Y gene does not produce marked effects on feeding, indicating that other pathways are also involved, but knocking out the neuropeptide Y gene in leptin-deficient *ob/ob* mice causes them to eat less and expend more energy than *ob/ob* controls that have intact neuropeptide Y genes.

**23. Which of the following is wrongly matched ?**

a. V1:Vascular smooth muscle
b. V2 : distal nephron
c. V3: Anterior pitutary
d. V4: CNS

**V4:CNS**

G protein-coupled **Vasopressin Receptors**

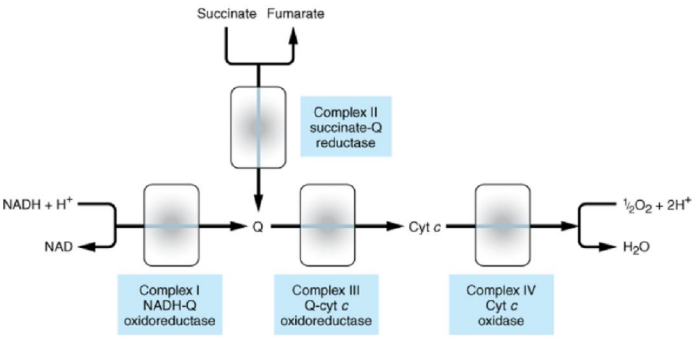
| | | | |
|---|---|---|---|
| V1A | vascular smooth muscle | phosphatidylinositol hydrolysis to increase the intracellular Ca2+ concentration. | cloned and typical serpentine receptors |
| V1B=V3 | Anterior pituitary | | |
| V2 | DCT | act through Gs to increase cAMP levels | |

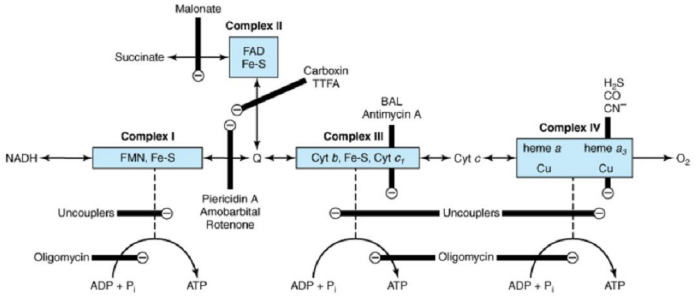
- **nephrogenic diabetes insipidus** that is due to loss of the ability of mutated V2 vasopressin receptors to mediate concentration of the urine
- Both oxytocin and ADH (vasopressin) are polypeptides, each containing nine amino acids. two hormones are almost identical except that in vasopressin, phenylalanine and arginine replace isoleucine and leucine of the oxytocin molecule

## Biochemistry

**24. Substance inhibiting transport of ADP from outside to inside and ATP from inside to outside across inner mitochondrial membrane :**

a. Atractyloside
b. Rotenone
c. Antimycin A
d. Oligomycin




**Uncouplers**

- dissociate oxidation in the respiratory chain from phosphorylation
- These compounds are toxic in vivo, causing respiration to become uncontrolled, since the rate is no longer limited by the concentration of ADP or $P_i$.
- The electrochemical potential difference across the membrane, once established as a result of proton translocation, inhibits further transport of reducing equivalents through the respiratory chain unless discharged

**Atractyloside**

**Mitochondria**

| | |
|---|---|
| Inner membrane | Electron carriers (complex I-IV)<br>ATP synthase<br>Membrane trasnporters |
| Matrix | TCA cycle enzymes<br>B-oxidation enzymes<br>Pyruvate dehydrogenase |
| Outer membrane | Acyl coA synthatase<br>Glycerolphosphate acyl transferase |

| **inhibitors of the respiratory chain:** | |
|---|---|
| Complex I | |
| ▪ **Barbiturates** (amobarbital)<br>▪ Piercidin A<br>▪ Roetenone | blocking the transfer from Fe-S to Q |
| **Complex II** | |
| ▪ **Malonate** | is a competitive inhibitor |
| Complex III | |
| ▪ **Antimycin A**<br>▪ (BAL)**dimercaprol** | |
| Complex IV | |
| ▪ **$H_2S$,**<br>▪ **Carbon monoxide**<br>▪ **Cyanide** | |
| Inhibitors of oxidative phosphorylation | |
| **Atractyloside** | inhibiting the transporter of ADP into and ATP out of the mitochondrion |
| **Uncouplers** | |
| Physiological:<br>**Thermogenin (or the uncoupling protein)** | brown adipose tissue that functions to generate body heat, particularly for the newborn and during hibernation in animals |
| **2,4-dinitrophenol** | |
| antibiotic **oligomycin** | by blocking the flow of protons through ATP |

by back-translocation of protons across the membrane through the ATP synthase. This in turn depends on availability of ADP and $P_i$.

Uncouplers (eg, dinitrophenol) are amphipathic and increase the permeability of the lipoid inner mitochondrial membrane to protons, thus reducing the electrochemical potential and short-circuiting the ATP synthase In this way, oxidation can proceed without phosphorylation.

| | |
|---|---|
| | synthase |

**25. Vitamin deficiency causing lactic acidosis :**

a. Riboflavin
b. Thiamine
c. Niacin
d. Pantothenic acid

**Thiamine**

- **Thiamin** has a central role in energy-yielding metabolism, and especially the metabolism of carbohydrates
- **Thiamin diphosphate** is the coenzyme for three multi-enzyme complexes that catalyze oxidative decarboxylation reactions:
  - **pyruvate dehydrogenase** in carbohydrate metabolism
  - **alpha-ketoglutarate dehydrogenase** in the citric acid cycle and
  - the **branched-chain keto-acid dehydrogenase** involved in the metabolism of leucine, isoleucine, and valine
- Thiamin diphosphate is also the coenzyme for **transketolase**, in the pentose phosphate pathway
- Thiamin deficiency can result in three distinct syndromes:
  - **a chronic** peripheral **neuritis**, **beriberi,** which may or may not be associated with heart failure and edema;
  - **acute pernicious (fulminating) beriberi (shoshin beriberi),** in which **heart failure** and metabolic abnormalities predominate, without peripheral neuritis;
  - **Wernicke's encephalopathy** with **Korsakoff's psychosis,** which is associated especially with **alcohol and narcotic abuse**.
  - The role of thiamin diphosphate in pyruvate dehydrogenase means that in deficiency there is impaired conversion of pyruvate to acetyl CoA. In subjects on a relatively high carbohydrate diet, this results in increased plasma concentrations of lactate and pyruvate, which may cause life-threatening **lactic acidosis**
- Thiamin Nutritional Status Can Be Assessed by **Erythrocyte Transketolase Activation** : The activation of apo-transketolase (the enzyme protein) in erythrocyte lysate by thiamin diphosphate added in vitro has become the accepted index of thiamin nutritional status.

**26. All of the following are essential micronutrients except :**

a. Lead

**Lead**

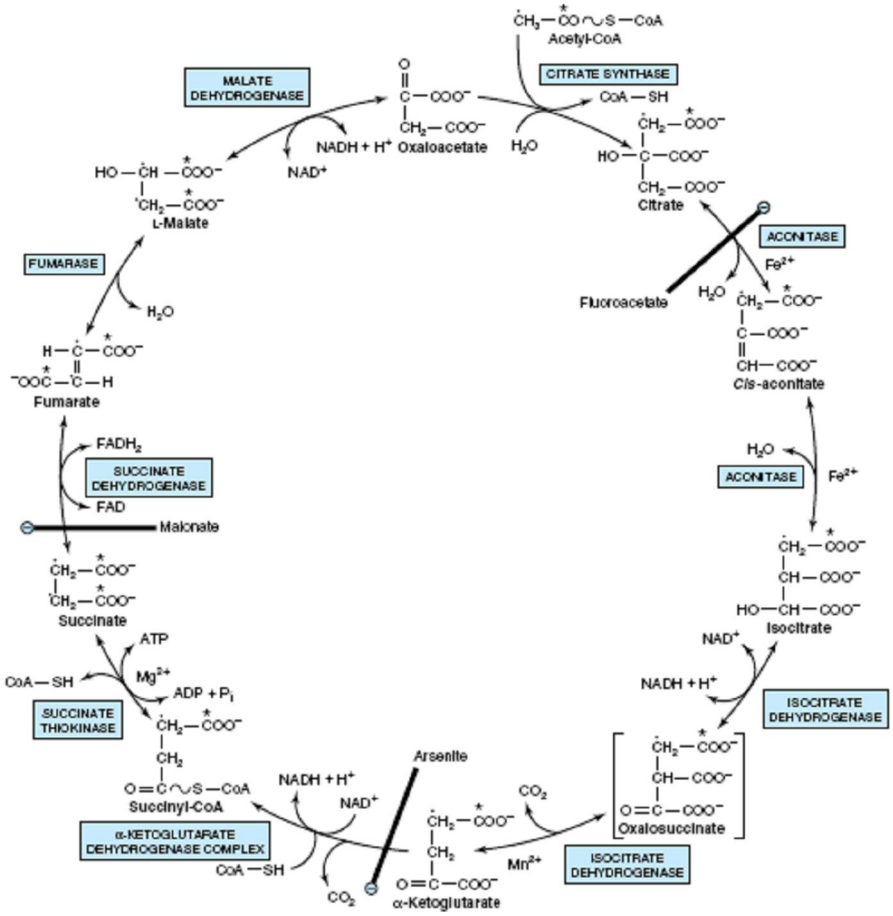
b. Iron
c. Maganese
d. Sodium

**27. Substance which combine with acetyl CoA and precipitates oxaloacetate inhibiting citric acid cycle :**

a. Malonate
b. Fumarate
c. Arsenite
d. Fluoroacetate

**Fluroacetate**

- Citrate is isomerized to isocitrate by the enzyme **aconitase** (aconitate hydratase);
- the reaction occurs in two steps:
- dehydration to *cis*-aconitate and rehydration to isocitrate.
- Although citrate is a symmetric molecule, aconitase reacts with citrate asymmetrically, so that the two carbon atoms that are lost in subsequent reactions of the cycle are not those that were added from acetyl-CoA.
- This asymmetric behavior is the result of **channelling**—transfer of the product of citrate synthase directly onto the active site of aconitase, without entering free solution.
- This provides integration of citric acid cycle activity and the provision of citrate in the cytosol as a source of acetyl-CoA for fatty acid synthesis.
- The poison **fluoroacetate** is toxic, because fluoroacetyl-CoA condenses with oxaloacetate to form fluorocitrate, which inhibits aconitase, causing citrate to accumulate




**28. In PKU main aim of first line therapy is :**

a. To replace deficient product
b. To reduce substrate for enzyme
c. Change in confirmation of enzyme
d. Supplementation of limiting aminoacid

**To reduce substrate for enzyme**

- **Phenylalanine.** Phenylalanine is first converted to tyrosine . Subsequent reactions are those of tyrosine
- **Hyperphenylalaninemias** arise from defects in
  - phenylalanine hydroxylase itself (**type I, classic phenylketonuria** or **PKU**), : PAH gene Chromosome 12q mutation
  - cofactor tetrahydrobiopterin (BH4) deficiency : in dihydrobiopterin reductase **(types II and III),** or in dihydrobiopterin biosynthesis **(types IV and V)**
- Alternative catabolites are excreted

- A **diet low in phenylalanine** can prevent the mental retardation of PKU (frequency 1:10,000 births). **.**
- The accumulation of phenylalanine inhibits the transport of other amino acids required for protein or neurotransmitter synthesis, reduces synthesis and increases degradation of myelin, and leads to inadequate formation of norepinephrine and serotonin.
- Phenylalanine is a competitive inhibitor of tyrosinase, a key enzyme in the pathway of melanin synthesis, and accounts for the hypopigmentation of hair and skin.
- Untreated children with classic phenylketonuria are normal at birth but fail to attain early developmental milestones, develop microcephaly, and demonstrate progressive impairment of cerebral function.
- Hyperactivity, seizures, and severe mental retardation are major clinical problems later in life.
- Electroencephalographic abnormalities; **"mousy" odor** of skin, hair, and urine (due to **phenylacetate** accumulation); and a tendency to hypopigmentation and eczema complete the devastating clinical picture.

| | | | |
|---|---|---|---|
| Phenylketonuria type I | Phenylalanine hydroxylase | Mental retardation, microcephaly, hypopigmented skin and hairs, eczema, "mousy" odor | AR |
| Phenylketonuria type II | Dihydropteridine reductase | Mental retardation, hypotonia, spasticity, myoclonus | |
| Phenylketonuria type III | 6-Pyruvoyl-tetrahydropterin synthase | Dystonia, neurologic deterioration, seizures, mental retardation | |
| GTP cyclohydrolase I deficiency | GTP cyclohydrolase I | Mental retardation, seizures, dystonia, temperature instability | |
| Carbinolamine dehydratase deficiency | Pterin-4 - carbinolamine dehydratase | Transient hyperphenylalaninemia (benign) | |

- **DNA probes** facilitate prenatal diagnosis of defects in phenylalanine hydroxylase or dihydrobiopterin reductase.
- Elevated blood phenylalanine may not be detectable until 3–4 days postpartum.
- False-positives in premature infants may reflect delayed maturation of enzymes of phenylalanine catabolism.
- An older and less reliable screening test employs $FeCl_3$ to detect urinary phenylpyruvate. $FeCl_3$ screening for PKU of the urine of newborn infants is compulsory in many countries, but in the United States has been largely **supplanted by screening by *tandem mass spectrometry***

Foods rich in phenhylalanine are : animal products (meat , fish , eggs ,), dairy products (cheese ,cow milk ) , starchy foods (potato , bread , pasta , corn) ,nuts , legumes , artificial sweeteners (aspartame= phenylalanine + aspartic acid) , diet soft drinks

- In contrast, affected children who are detected and treated at birth show none of these abnormalities
- To prevent mental retardation, diagnosis and initiation of dietary treatment of classic phenylketonuria must occur **before the child is 3 weeks of age**. For this reason, most newborns are screened by determinations of blood phenylalanine levels. Abnormal values are confirmed using quantitative analysis of plasma amino acids.
- Dietary phenylalanine restriction is usually instituted if blood phenylalanine levels are **>250 micromol/L (4 mg/dL).**
- Treatment consists of a special **diet low in phenylalanine** and **supplemented with tyrosine**, since tyrosine becomes an essential amino acid in phenylalanine hydroxylase deficiency.
- With therapy, plasma phenylalanine concentrations should be maintained between 120 and 360 micro mol/L (2 and 6 mg/dL).
- Dietary restriction should be continued and monitored indefinitely.
- Some patients with **milder forms** of phenylketonuria (phenylalanine <1200 microm at presentation) show increased tolerance to dietary proteins and **improved metabolic control when treated with tetrahydrobiopterin (5–20 mg/kg per day), an essential cofactor of phenylalanine hydroxylase**
- A number of women with phenylketonuria who have been treated since infancy will reach adulthood and become pregnant. If maternal phenylalanine levels are not strictly controlled before and during pregnancy, their **offspring are at increased risk for congenital defects and microcephaly (*maternal phenylketonuria*).** After birth, these children have severe mental and growth retardation.
- Pregnancy risks can be minimized by continuing lifelong phenylalanine-restricted diets and assuring strict phenylalanine restriction 2 months prior to conception and throughout gestation

**29. Vitamin K dependent clotting factor :**

a. VII
b. I
c. VIII
d. XII

**VII**

Vit k dependent

- clotting factors: Factor 2 (prothrombin) , 7 , 9 , 10 & protein C,S,Z
- bone metabolism : BGP (bone GIa protein ) MGP (Matrix GIa protein)

**30. in duchene's muscular dystrophy if there is a mutation in the promoter region of the gene coding for dystrophin would affect :**

a. initiation of transcription of dystrophin gene
b. termination of transcription of dystrophin gene
c. capping of mRNA of dystrophin gene
d. tailing of mRNA of dystrophin gene

**initiation of transcription of dystrophin gene**

promoter sequence in a transcription unit at 5' end of coding strand is of 2 ypes :

1. fidelity promoter : guides RNA polymerase II to +1 site from where it should start transcription
2. frequency promoter : guides RNA polymerase as how many times the gene has to be transcribed under basal conditions

mutation in promoter sequence → affect initiation of transcription.

**31. All of the following are methods for gene transfer except :**

a. Transfection
b. Electroporation
c. FISH
d. Site directed recombination

**FISH**

Transfection = non-viral methods in introduction of nucleic acid by creating pores/holes in cell membrane
Chemical based transfection using:

- Calcium phosphate
- Highly branched organic compounds (dendrimers)
- Cationic liposomes
- Cationic polymers (DEAE dextran /polyethylenimine)

Non-chemical transfection :

- Electroporation
- Sono-poration
- Optical transfection
- Gene electrotransfer
- Impalefection (use nanofiber)

Particle based methods :

- Gene gun
- Magnetofection
- Impalfection

Viral methods :Transduction
Transformation
Conjugation

**32. A 3 day old newborn fail to take feeds , vomiting and protruded belly. Which of the following reducing sugar is present in urine giving benedict's test positive ?**

a. Glucose
b. Fructose
c. Sucrose
d. Galactose

| | |
|---|---|
| Galactose 1-phosphate **uridyl transferase** | Vomiting, **hepatomegaly, jaundice, cataracts**, amino aciduria, failure to thrive |
| **Galactokinase** | **Cataracts** |
| Uridine diphosphate galactose 4-**epimerase** | Similar to transferase deficiency with additional findings of **hypotonia and nerve deafness** |

Newborn – breast fed – breast milk has lactose = galactose + glucose

## Forensic Medicine

**33. Spanish windlass is :**

a. Hanging
b. Mugging
c. Bansdola
d. Garotting

**Garotting :**

- Person is attacked from behind & a ligature is thrown around neck & quickly tightened by twisting it with a lever
- Modification : neck forced against a sharp spike penetrating spinal cord
- Was used in spain as mode of execution
- An iron collar around neck is tightened by screw for strangling : spainsh windlass

Bansdola : strangulation of neck by using bamboo sticks one infront and one behind neck

Mugging : strangulation of neck by using bend of elbow

**34. 6 yr old child was run over by vehicle while playing roadside. Tyre marks on his thigh are example of :**
a. Patterned bruise
b. Imprint abrasion
c. Patterned abrasion
d. Ectopic bruise

**Patterned bruise**

**35. Widmark's formula is used for estimation of :**
a. alcohol level
b. Time since death
c. Essence of crime
d. Stature of dead body

**Alcohol level :**

Widmark's formula for Blood alchol
A = PRC
A: weight (gram) of alcohol in body
P: body weight (Kg)
R: constant (0.6 for men & 0.5 for women)
C: concentration of alcohol in blood (mg/kg)
Widmarks formula for urine alcohol
A=3/4 PRC
C: concentration of alcohol in urine (mg/kg)

**36. Young boy presented with increased salivation , lacrimation , sweating , diarrhea , abdominal pain . most likely diagnosis is withdrawl of ?**
a. Cocaine
b. Heroin
c. LSD
d. Marijuana

**Heroin = opioid withdrawl**

**37. All can occur in aluminium phosphide ingestion except :**
a. Phosgene gas liberation
b. Subendocardial hemorrhage
c. Cyt P450 inhibition
d. Esophageal stricture

**Esophageal stricture**

Aluminium phosphide (pesticide/insecticide/rodenticide) → moisture → phophine gas → inhibit Respiratory chain enzymes (cytP450) & cytotoxic action : affects all organs of body
CVS : congestion (subendocaridal hemorrhage) , edema , fragmentation of fibers , focal necrosis , leucocyte infiltration

**38. A 24 years male presents with tachycardia , bronchodilation , constipation , high temperature. Most likely he is poisoned with :**
a. Organophosphorous
b. Atropine
c. Penicillamine
d. Mushroom

**Atropine = dhatura**

**39. A young female ingested amitryptiline with intention of suicide. All of the following is done in management except:**
a. Give atropine as antidote

**Atropine as antidote**

Amitryptiline is anticholinergic : so in its poisoning you can't give another anticholinergic – atropine as antidote

b. Injection diazepam for convulsions
c. Gastric lavage
d. Sodium bicarbonate for metabolic acidosis

Management :
Supportive : Gastric lavage – respiratory support – fluids – bicarbonate for acidosis
Diazepam i.v. for convulsions and delirium
Propanolol /lignocaine for cardiac arrhythmia (MImp)

**40. All can produce central respiratory paralysis except :**
a. Opium
b. Strychnine
c. Barbiturates
d. Gelselium

**Strychnine**

It acts on spinal cord : postganglionic recpetors for ant motor horn cells – prevent glycine (inhibitory transmitter) action → release excitation

## Pathology

**41. All are pale infarcts except :**
a. Heart
b. Spleen
c. Kidney
d. Lung

**Lung**

**Red infarcts**
- with **venous occlusions** (such as in **ovarian torsion)**
- in **loose tissues** (such as **lung**) that allow blood to collect in the infarcted zone;
- in tissues with **dual circulations** such as **lung** and **small intestine**, permitting flow of blood from an unobstructed parallel supply into a necrotic area (such perfusion not being sufficient to rescue the ischemic tissues);
- in tissues that were **previously congested** because of sluggish venous outflow
- when **flow is re-established** to a site of previous arterial occlusion and necrosis (e.g., fragmentation of an occlusive embolus or angioplasty of a thrombotic lesion).

**White infarcts**
- occur with **arterial occlusions** or
- in **solid organs** (such as heart, spleen, and kidney), where the solidity of the tissue limits the amount of hemorrhage that can seep into the area of ischemic necrosis from adjoining capillary beds

**42. in wegners granulomatosis MC renal lesion is :**
a. interstitial granuloma
b. granuloma in blood vessel wall
c. focal necrotising GN
d. diffuse GN

**Focal necrotizing GN**

Wegener granulomatosis is a necrotizing vasculitis characterized by a triad of

- *Acute necrotizing granulomas* of the upper respiratory tract (ear, nose, sinuses, throat) or the lower respiratory tract (lung) or both
- *Necrotizing or granulomatous vasculitis* affecting *small to medium-sized vessels* (e.g., capillaries,

venules, arterioles, and arteries), most prominent in the lungs and upper airways but affecting other sites as well

- Renal disease in the form of ***focal necrotizing***, *often* ***crescentic***, *glomerulonephritis*

**43. Bad prognostic factor for AML :**

a. Monosomy
b. Deletion of X or Y
c. t(8,21)
d. nucleophosmin gene mutation

**Monosomy**

AML prognostic factors :

| **Favourable** | Unfavourable |
|---|---|
| <55 yrs | >60 yrs |
| Denovo | Secondary |
| WBC <25000/microL | >1,00,000 /microL |
| WHO subtype :<br>Corebinding factor AML | AML with multilineage dysplasia<br>Therapy related AML<br>Acute megakaryocytic leukemia<br>Acute erythroid leukemia<br>Acute basophilic leukemia |
| FAB type :<br>M3, M4Eo | M0 , M5a, M5b , M6 , M7 |
| t(15,17) **, t(8,21)** , inv (16)<br>normal cytogenetics | Chromosome 5 & 7 deletions /monosomy<br>Multiple (>3) anomalies :hyperploidy<br>11q23<br>T(6,9) |
| No auer rods<br>No extramedullary ds | Auer rods<br>Extramedullary ds |
| CD34 - | CD34 + , CD 56+ |
| **Nucleophosmin 1 (NPM-1)** | High LDH , low bilirubin<br>Kit mutations<br>FLT-3 interanl tandem repeat duplication<br>MDR-1 expression |

**44. all are associated with subendocardial hemorrhages except:**

a. seen in right ventricle
b. can be seen in patients with head injury
c. occur in form of continuous sheet
d. flame shaped confluent hemorrhage

**Seen in right ventricle**

Subendocardial – flame shaped confluent – hemorrhages – in one continous sheet – common in Left ventricle /left side of IV septum and on opposing papillary muscle
Seen in

- Severe hypotension/shock
- ICH (head injury) , cerebral edema , tumors

- Ectopic pregnancy , ruptured uterus , APH , PPH , abortion
- Arsenic poisoning

**45. All are inflammatory mediator except :**

a. IFN
b. TNF
c. PG
d. Myeloperoxidase

**Myeloperoxidase**

| Mediator | Principal Sources | Actions |
|---|---|---|
| **CELL-DERIVED** | | |
| Histamine | Mast cells, basophils, platelets | Vasodilation, increased vascular permeability, endothelial activation |
| Serotonin | Platelets | Vasodilation, increased vascular permeability |
| Prostaglandins | Mast cells, leukocytes | Vasodilation, pain, fever |
| Leukotrienes | Mast cells, leukocytes | Increased vascular permeability, chemotaxis, leukocyte adhesion and activation |
| Platelet-activating factor | Leukocytes, mast cells | Vasodilation, increased vascular permeability, leukocyte adhesion, chemotaxis, degranulation, oxidative burst |
| Reactive oxygen species | Leukocytes | Killing of microbes, tissue damage |
| Nitric oxide | Endothelium, macrophages | Vascular smooth muscle relaxation, killing of microbes |
| Cytokines (TNF, IL-1) | Macrophages, endothelial cells, mast cells | Local endothelial activation (expression of adhesion molecules), fever/pain/anorexia/hypotension, decreased vascular resistance (shock) |
| Chemokines | Leukocytes, activated macrophages | Chemotaxis, leukocyte activation |
| **PLASMA PROTEIN–DERIVED** | | |
| Complement products (C5a, | Plasma (produced in | Leukocyte chemotaxis and |

| | | |
|---|---|---|
| C3a, C4a) | liver) | activation, vasodilation (mast cell stimulation)<br>Increased vascular permeability, smooth muscle contraction, vasodilation, pain<br>Endothelial activation, leukocyte recruitment |
| Kinins | Plasma (produced in liver) | |
| Proteases activated during coagulation | Plasma (produced in liver) | |

**46. Rate of minerlisation of newly formed osteoid is labeled by (repeat) :**

a. Vonkosa stain for calcium
b. Alizarin red
c. Tetracycline labeling
d. Fluroscence

**Tetracycline labling**

**47. Initiating event in endotoxic shock is :**

a. Peripheral vasodilation
b. Endothelial injury
c. Volume depletion
d. Reduced cardiac output

**Endothelial injury**

**48. Onion bulb appearance of nerve are seen in :**

a. Amyloid angiopathy
b. CIDP
c. Diabetic neuropathy
d. Leprosy

**CIDP**

**Chronic Inflammatory Demyelinating Polyradiculoneuropathy**

- **symmetric**, **mixed sensorimotor** polyneuropathy.
- Clinical remissions may occur with **steroid treatment and plasmapheresis.**
- Biopsies of sural nerves show evidence of recurrent demyelination and remyelination associated with well-developed **onion bulb structures.**

**49. All are true about GIST except :**

a. MC site is duodenum
b. Well circumscribed
c. Ulceration and necrosis
d. PET scan is useful in securing response to therapy

**MC site duodenum**

Types of mesenchymal tumors :

- smooth muscle tumors are called *leiomyomas* or *leiomyosarcomas*,
- nerve sheath tumors are termed *schwannomas*, and
- those resembling glomus bodies in the nailbeds and at other sites are termed *glomus tumors*
- ***GI stromal tumor (GIST)*** is the most common mesenchymal tumor of the abdomen, and more than half of these tumors occur in the **stomach**.

Epidemiology.

- **males.**
- **60 years,** with fewer than 10% occurring in individuals under 40 years of age.
- Of the uncommon GISTs in **children**, some are related to the ***Carney triad,*** a nonhereditary syndrome seen primarily in **young females** that includes **gastric GIST,**

**paraganglioma, and pulmonary chondroma**.

- There is also an increased incidence of GIST in individuals with **neurofibromatosis type 1**

- Pathogenesis.
- Approximately *75% to 80% of all GISTs have oncogenic, gain-of-function mutations of the gene encoding the* ***tyrosine kinase c-KIT,*** which is the receptor for stem cell factor.
- Approximately 8% of GISTs have mutations that activate a related tyrosine kinase, **platelet-derived growth factor receptor α (PDGFRA).**
- In sporadic GISTs, *c-KIT* and *PDGFRA* gene mutations are mutually exclusive.
- GISTs appear to arise from, or share a common stem cell with, **the interstitial cells of Cajal,** which are located in the **muscularis propria** and serve as **pacemaker cells for gut peristalsis**. Like GISTs, **Cajal cells express c-KIT (also known as CD117) and CD34.**
- Interestingly, familial GIST, which is rare, is associated with germline *c-KIT* or *PDGFRA* mutations; these patients, who develop multiple GISTs, may also have diffuse hyperplasia of Cajal cells.
- Mutation of *c-KIT* or *PDGFRA* is an early event in sporadic GISTs and is detectable in lesions as small as 3 mm.
- The constitutively **active c-KIT and PDGFRA receptor tyrosine kinases** produce intracellular signals that **activate the RAS and PI3K/AKT pathways** and thereby promote tumor cell proliferation and survival.

- **Morphology**.
- Primary gastric GISTs can be quite
- **large,** as much as 30 cm in diameter.
- They usually form a **solitary,**
- **well-circumscribed,** fleshy mass
- covered by **ulcerated or intact mucosa**
- but can also project outward toward the serosa.
- Metastases may take the form of multiple serosal nodules throughout the peritoneal cavity or as one or more nodules in the liver;
- spread outside of the abdomen is uncommon.
  - GISTs composed of thin elongated cells are classified as **spindle cell type**
  - whereas tumors dominated by epithelial-appearing cells are termed **epithelioid type**;
  - mixtures of the two patterns also occur.
- The most useful diagnostic marker is c-KIT, which is immunohistochemically detectable in 95% of gastric GISTs.

Clinical Features.

- Symptoms of GISTs at presentation may be related to **mass effects.**
- **Mucosal ulceration** can cause **blood loss**, and approximately half of individuals with GIST present with **anemia** or related symptoms.
- GISTs may also be discovered as an incidental finding during radiologic imaging, endoscopy, or abdominal surgery performed for other reasons.
- **Complete surgical resection is the primary treatment**

**for localized gastric GIST**.

- The prognosis correlates with tumor size, mitotic index, and location, *with* ***gastric GISTs being somewhat less aggressive than those arising in the small intestine***.
- Recurrence or metastasis is rare for gastric GISTs under 5 cm but common for mitotically active tumors larger than 10 cm.
- Patients with **unresectable, recurrent, or metastatic** disease often respond to ***imatinib,*** a tyrosine kinase inhibitor that inhibits c-KIT and PDGFRA, and is also effective in suppressing BCR-ABL kinase activity in chronic myeloid leukemia
- Development of resistance to imatinib is most often related to secondary *c-*
- *KIT* mutations that limit drug efficacy.

**50. All are true regarding bacterial killing except :**

a. Chediak-higashi syndrome : defective phagolysosome formation
b. Bruton's aggamagloulinemia : opsonization is not defective
c. Myeloperoxidase acts by generating HOCl ions
d. NADPH oxidase acts by generating superoxide radicals

**Bruton's aggamagloulinemia : opsonization is not defective**

**X-Linked Agammaglobulinemia (Bruton's Agammaglobulinemia)**

- *It is characterized by the* ***failure of B-cell precursors (pro-B cells and pre-B cells) to develop into mature B cells***.
- During normal B-cell maturation in the bone marrow, the Ig heavy-chain genes are rearranged first, in pre-B cells, and these are expressed on the cell surface in association with a "surrogate" light chain, where they deliver signals that induce rearrangement of the Ig light-chain genes and further maturation.
- This need for Ig-initiated signals is a quality control mechanism that ensures that maturation will proceed only if functional Ig proteins are expressed.
- X-linked agammaglobulinemia is caused by mutations in a cytoplasmic tyrosine kinase, called ***Bruton tyrosine kinase (Btk);*** the gene that encodes it is located on the **long arm of the X chromosome** at **Xq**21.22.
- Btk is a protein tyrosine kinase that is associated with the Ig receptor complex of pre-B and mature B cells and is needed to transduce signals from the receptor. When it is mutated, the pre-B cell receptor cannot deliver signals, and maturation stops at this stage.
- Because light chains are not produced, the complete antigen receptor molecule (which contains Ig heavy and light chains) cannot be assembled and transported to the cell membrane.
- As an X-linked disease, this disorder is seen almost **entirely in males**,
- but **sporadic cases** have been described in **females,** possibly caused by mutations in some other gene that functions in the same pathway.
- The classic form of this disease has the following characteristics:
  - B cells are absent or markedly decreased in the
- *The disease usually* ***does not become apparent until about 6 months of age, as maternal immunoglobulins are depleted.***
- In most cases, **recurrent bacterial infections of the respiratory tract,** such as acute and chronic pharyngitis, sinusitis, otitis media, bronchitis, and pneumonia, call attention to the underlying immune defect.
- Almost always the causative organisms are *Haemophilus influenzae*, *Streptococcus pneumoniae*, or *Staphylococcus aureus*. These organisms are normally opsonized by antibodies and cleared by phagocytosis.
- Because antibodies are important for neutralizing infectious viruses that are present in the bloodstream or mucosal secretions or being passed from cell to cell,
- individuals with this disease are also susceptible to certain viral infections, especially those caused by **enteroviruses, such as echovirus, poliovirus, and coxsackievirus**.
- These viruses infect the gastrointestinal tract, and from here they can disseminate to the nervous system via the blood. Thus, immunization with live poliovirus carries the risk of paralytic poliomyelitis, and echovirus can cause fatal encephalitis.
- For similar reasons, ***Giardia lamblia***, an intestinal protozoan that is normally resisted by secreted IgA, causes persistent infections in persons with this disorder. \
- In general, however, most intracellular viral, fungal, and protozoal infections are handled quite well by the intact T cell–mediated immunity.
- **Autoimmune diseases**, such **as arthritis and dermatomyositis**, occur with increased frequency, in as many as 35% of individuals with this disease, which is **paradoxical** in the presence of an immune deficiency.
- It is likely that these autoimmune disorders are caused by a breakdown of self-tolerance resulting in autoimmunity, but chronic infections associated with the immune deficiency

circulation, and the serum levels of all classes of immunoglobulins are depressed. Pre-B cells, which express the B-lineage marker CD19 but not membrane Ig, are found in normal numbers in the bone marrow.

- Germinal centers of lymph nodes, Peyer's patches, the appendix, and tonsils are underdeveloped.
- Plasma cells are absent throughout the body.
- T cell–mediated reactions are normal.

may play a role in inducing the inflammatory reactions.

- The treatment of X-linked agammaglobulinemia is **replacement therapy with immunoglobulins.**
- In the past, most patients succumbed to infection in infancy or early childhood. Prophylactic intravenous Ig therapy allows most individuals to reach adulthood

**51. True about fibronectin nephropathy are all except :**

a. Autosomal recessive
b. Subendothelial mesangial deposits
c. PAS & trichrome positive mesangial deposits
d. Inconsistent IgG deposits

**Autosomal recessive**

Fibronectin nephropathy :

- **Autosomal dominant**
- Atypical lobular GN : **nonamyloid (congored negative) nonimmunoglobulin** , **PAS & trichrome positive subendothelial & mesangial**- focally fibrilar – electron dense large giant **fibronectin organized deposits** – that **don't stain for Ig and complement** → Glomerular enlargement & lobulation
- MC presentation : proteinuria

**52. Nephrocalcinosis in systemic granulomatous disorder is due to :**

a. Dystrophic calcification
b. Altered calcium sensing receptor
c. Excess vit D absorption
d. Extra renal conversion of 1,25 OH2 cholecalciferol

**Extra renal conversion of 1,25 OH2 cholecalciferol**

The mechanism of abnormal calcium metabolism is increased production of 1,25-dihydroxyvitamin D by the granuloma itself

**53. Cytogenetics is difficult in solid tumors like Carcinoma cervix due to :**

a. High mitotic activity
b. Good quality metaphase
c. Inadequate specimen
d. Often contaminated and infested with infective microroganisms

**Often contaminated and infested with infective microorganisms**

Cytogenetics of solid tumors by FISH doesnot require dividing cells or metaphase nuclei : high mitotic activity and metaphase are not a problem
Sample is usually adequate in tissue biopsy
Bacterial contamination is a common problem in isolation and extraction of DNA from clinical samples

## Microbiology

**54. What will happen if bacteria acquires genes coding for**

**Bacteria will die due to deficiency of methylase**

**restriction endonuclease :**

a. Bacteria will die due to deficiency of methylase
b. Damage the host cell
c. Bacteria will divide and multiply many times
d. Enahance proof reading activity of that bacteria

- Restriction endonuclease cut DNA at specific recognition nucleotide sequence (=called restriction sites).
- These enzymes in bacteria provide defence against viruses.
- Inside bacterial host these enzymes cut up foreign viral DNA
- Bacterial DNA is protected by mehtylation (by modification enzyme methylase) against restriction endonuclease
- DNA methyltransferase = methylase : methylate cytosine and adenine residues in DNA
- If bacteria laks these methylase – their own DNA gets cut up by restriction enzymes and bacterial will die

Types of restriction endonucleases :

| type | Cleaves at | Cofactors required | Subunits |
|---|---|---|---|
| I | Site remote from recognition site | ATP<br>S-adenosyl-methionine (SAM) | 3 subnits<br>HsdR : restriction<br>HsdM : methylase<br>HsdS :Specificity of cut site recognition + methylase |
| II (MC) | Within or at short specific distance from recognition sites | | Only restriction<br>No methylase activity |
| III | Short distance from recognition site | Requires ATP but doesn't hydrolyse it<br>SAM : stimulates reaction but not required. Exists as a part of complex with a modification methylase | |
| IV | Targets methylated DNA | | |

**55. Malignant pustule is (repeat)**

a. Squamous cell carcinoma
b. Malignant melanoma
c. Anthrax
d. Infected rodent ulcer

**Anthrax**

**56. All are true about clostridium tetani infection except :**

a. Soil and intestine are main reservoir
b. Trauma and contaminated wound are main modes of transmission
c. Herd immunity is not of much value
d. Seen commonly in winter & dry climate

**Seen commonly in winter & dry climate**

- As tetanus is not a contagious disease , herd immunity is of no use.
- Tetanus has more mortality in neonates in wet seasons

**57. All are true about Hemophilus except (repeat)**

a. Favtor X & V are required for growth
b. H.influenza b is not a major cause of infection in child <2 months
c. Protein capsule is responsible for virulence

**Protein capsule is responsible for virulence**

Capsule is polysaccharide of pentose sugars

H.influenza : 1st free living organism tohave its entire genome sequenced.

| | |
|---|---|
| H.influenza | Factor X (heat stable) & V(heat labile) |

d. Mc invasive disease is meningitis

| | |
|---|---|
| H. hemolyticus | |
| H.parainfluenza | Factor V |
| H.aprophilus | Factor X |

**58. False about clostridium perfringenes (repeat)**
a. Hyaluronidase is major cause of toxicity
b. MC cause of gas gangrene
c. Food poisoning strains produce heat resistant spores
d. Normally present in human feces

**Hyaluronidase is major cause of toxicity**
Alpha toxin = lecithinase is a major toxin

**59. Characteristic of bacillus cereus infection:**
a. Absent vomiting
b. Absent diarrhea
c. Abdominal pain
d. Fever

**Abdominal pain**
- Bacillus cereus
  - Emetic form (1-5 hrs)
  - Diarrheal form (8-16 hrs): abdominal pain is a feture
- Fever is absent in both the forms

**60. A child with pustular lesions on leg . pus c/s gives beta hemolytic bacitracin sensitive bacteria . correct statement about this organism is :**
a. Foot infection causative agent is of group D type
b. M protein of both pharyngeal and skin variety are same
c. C carbohydrate is different for pharyngitis causing strain
d. MecA gene is related to it

**Foot infection causative agent is of group D type**
- Beta hemolytic bacitracin sensitive = strep pyogenes
- Group D streptococci = wound infection , IE , septicemia , UTI
- Higher mumbered M type : skin lesions
- Lower numbered M types : pharyngitis
- M protein for skin and phyrangeal variety is different
- C carbohydrate is a group specific antigen : same for all B hemolytic strep (A to V except I,J) : cannot distinguish between phyrngitis and skin infection
- Mec A gene coding for PBP2A transpeptidase : is related to MRSA , coaulase negative staph , pneumococci

**61. MC cause of IE in patient with prosthetic valve after 8 months of surgery :**
a. Streptococcus viridians
b. Streptococcus epidermidis
c. Staphylococcus epidermidis
d. HACEK

**Staphylococcus epidermidis**

| | |
|---|---|
| Native valve IE<br>i.v. drug users IE | Staphylococcus aureus |
| Early prosthetic valve IE<br>(0-12 months) | Coagulase negative staph |
| Late prosthetic valve IE<br>(>12 months) | Viridians streptococci |

**62. BM transplant recipient developed chest infection. CXR shows "tree in bud" appearance. Causative agent is:**
a. P.carinii
b. RSV
c. Klebseilla
d. M.TB

**M.TB**
- Tree in bud = airway plugging
- Infection spreading endobronchially : TB & bronchopneumonia
- Bronchectasis in cystic fibrosis

**63. Genetic reassortment is a feature of :**
a. Hepdna
b. Rota virus
c. Herpes
d. Astro virus

**Rota virus**
- Genetic reassortment = mixing of genetic material into new combinations
- Mechanisms : chromosome assortment , chromosomal crossover
- Seen in : rota virus & influenza virus

**64. All are correct about varicella virus except :**
a. 10-30% recurrence rate
b. Rash on flexor aspect
c. All stages of rash seen at one time
d. SAR 90%

**10-30% recurrence rate > rash on flexor aspect**

Varicella :
- Variable rate of recurrence
- Rash on face and trunk than to limbs
- Pleomorphic rash : all stages at one time
- SAR : 75-90%

**65. Mode of transmission of amoebiasis all except :**
a. Fecooral
b. Oro rectal
c. Vertical transmission
d. Cockroaches

**Vertical transmission**

**66. Sputum is sterilized by all except :**
a. Boiling
b. Autoclaving
c. Cresol
d. Chlorheximide

**Chlorheximide**

Disinfection of sputum :
Best method : Autoclave > boiling/incineration >phenol (cresol)

**67. Indicator used for plasma sterilization**
a. B.pumilis
b. B.sterothermophilus
c. B.subtilis
d. Cl.tetani

**B.sterothermophilus**

Plasma sterilization :
Method = ethylene oxide
Indicator = B.sterothermophilus > B. subtilis

**68. True of ETEC :**
a. Cause disease by mucosal invasion
b. Common cause of acute watery diarrhea in children of developing countries
c. Not a common cause of traveller's diarrhea
d. Spread by person to person or fomites

**Spread by person to person or fomites**

**69. Vi polysaccharide vaccine :**
a. Has many A/e
b. Has many C/I
c. Has local S/e
d. Can be combined with vaccines like Hepatitis B & yellow fever

**Can be combined with vaccines like Hepatitis B & yellow fever**

Vi CPS = Vi Capsular polysaccharide vaccine
- Minimal age : 2 yrs
- Poorly immunogenic in <5 yr child (d/t T cell independent properties)
- 3 yr Efficacy 55% (compared to 70% of whole cell & 51% of ty21a)
- Less S/e & C/I compared to whole cell vaccine
- Yellow fever vaccine doesn't interfere if given together

- Can be administered simultaneously/at anytime before or after a parenteral live vaccines (MMR , VZV , yellow fever , HBV)

**70. A 25 yr male c/o headache , neck stiffness , fever . h/o of painless ulcer over penis 2 yrs back following which he developed mucocutaneous lesions. He was given antibiotic treatment. Which of the following will help in assessment of treatment response:**

a. VDRL
b. FTA ABS
c. TPHA
d. Dark field microscopy

**VDRL**

**71. False regarding Spaulding classification for disinfection of item :**

a. Semi critical equipments are those which come in contact with mucosa and intact skin
b. Cardiac catheter is an example of critical equipment
c. Semi critical equipments require low level of disinfection
d. Non critical equipments require only decontamination

**Semi critical equipments require low level of disinfection**

**Spaulding's classification :**

| Equipment | Definition | Processing | Examples |
|---|---|---|---|
| Critical | Enters sterile tissue including vascular system | Cleaning → sterilization | • Sx instruments<br>• Foot care Equipments<br>• Endoscopes<br>• Eye & dental equipments |
| **Semi critical** | **Contact (not penetration) with mucosa or intact skin** | **Cleaning → high level disinfection** (as minimum sterilization is preferred) | • Laryngoscopes<br>• Anesthesia equipments<br>• Specula<br>• Tonometer<br>• USG probes<br>• Ear cleaning equipments<br>• Breastpump accessories<br>• Fingernail care<br>• [in short equipments used on multiple clients] |
| **Non critical** | Touches only intact skin / not directly touch the client | **Cleaning alone or f/b → low level disinfection** | • Stethoscopes<br>• BP cuffs<br>• ECG<br>• Scales<br>• Thermometers |

**72. False regarding hepatitis B :**

a. Outcome is age dependent
b. Vertical transmission is more important than horizontal
c. Period of communicability is long for several months
d. Virus can be identified 1 month before onset of jaundice

Vertical transmission is more important than horizontal

## Pharmacology

**73. Which of the following is least useful in overactive bladder syndrome :**

a. Fluvoxate
b. Darifenacine
c. Oxybutinin Hcl
d. Duloxetine

**Duloxetine**

**Overactive bladder syndrome :**

- **= urge incontinence**
- **Detrusor overactivity**
- Rx:
  - Fluid and coffee restriction
  - Bladder retraining

- Antimuscarinic drugs
  - **Darifenacin**
  - Hyoscyamine
  - **Oxybutynin**
  - Toltoredine
  - Solifenacine
  - Trospium **flavoxate**
- Devices : urgent PC neuromodulator
- Intravesical botulinum toxinA

**74. Not true about Ramelton :**
a. Acts on MT-1 &2 receptors
b. Recently approved for insomnia
c. Metabolized by cyp450
d. High addiction liability

**High addiction liability**

Ramelton :
- Melatonin recptor agonist
- Affinity for **both MT-1 & MT-2 receptors** in Suprachiasmatic nucleus → promote sleep by melatonin
- Not act on MT-3 recptors in GIT
- Not act on GABA-A recptors : no muscel relaxant/amnestic/anxiolytic potential
- **No dependence/abuse potential**
- **Use : delayed sleep onset (insomnia)**
- **Metabolized by Cyp 450** → metabolite M-II (less potent than parent compound) but has weak affinity for 5-HT2B receptor

**75. SERM Drug used for postmenopausal osteoporosis :**
a. Raloxifene
b. Estrogen
c. DES

**Raloxifene**

**Osteoporosis :**
ANTIREORPTIVE DRUGS :
- **Bisphosphonate : 1st line Rx**
  - **Alendronate**
  - **Risedronate**
- **SERM :** selective estrogen receptor modulator
  - Usually Stimulates osteopblast activity
  - **Raloxifene :** inhibit bone resoprtion by osteoclasts (also reduce risk for Breast Ca) – s/e : Hot flushes
- **Calcitonin :** inhibit osteoclastic bone reorption

BONE ANABOLIC AGENTS
- **Teripratide : recombinant PTH :** for severe osteoporosis not tolerating bisphosphonates - C/I in previous RT/padget's /young patients
- **Calcium salts**
- **Sodium fluoride**

- **RANK ligand inhibitors : Donesumab** – fully human monoclonal Ab – mimics activity of osteoprotegrin – binds to RANKL and preventing it to bind to RANK – thus reducing bone resorption

DUAL ACTION BONE AGENTS:

- **Strontium ranelate :** stimulate osteoblast & inhibits osteoclast **–** No GI s/e (MC cause of medication withdrwal in osteoporosis) **–** water soluble – ionized in stomach – doesn't inhibit bone recycling like bisphosphonates – not taken with food /calcium (competition for uptake)

**76. Rx of hormone responsive breast ca:**

a. Tamoxifen
b. Clomiphene citrate
c. Estrogen

**Tamoxifen**

Treatment of ER+ breast Cancers:

| ER recptor blocker | Aromatase inhibitors |
|---|---|
| **Tamoxifene** | Letrazole/anastrazole |
| **Pre & post menopausal women** | For post menopausal women only |
| Both early & advanced Ca | |
| MC hormonal Rx for male breast Ca | |
| Reduce C/L breast Ca | |

Treatment of ER- breast Cancers:
Chemotherapy
Monoclonal Ab against HER-2

**77. A patient in ICU with fever since 1 week was given amikacin & ceftriaxone empirically . after 48 hrs blood culture report shows kleibeilla with ESBL. Next step is :**

a. Increase dose of same antiniotics
b. Change amikacin to quinolone
c. Change ceftriaxone to imipenem
d. Change ceftriaxone to ceftazidime

**Change ceftriaxone to imipenem**

**78. Patient on long term treatment with methotrexate found to be resistant . mechanism of resistance :**

a. Deficiency of thymidylate kinase
b. Deficiency of thymidine kinase
c. Overproduction of dihydrofolate reductase
d. Deficiency of folate reductase

**Overproduction of dihydrofolate reductase**

**79. True about beta blockers in CHF except :**

a. Start at optimum dose
b. Precautions in NYHA 3 &4
c. Start at low dose and increase gradually over weeks
d. Metoprolol and carvedilol are preferred

**Start at optimum dose**

**80. To prepare NS from 10% dextrose (per 100 ml)**
a. 20 ml 10% D + 80 ml NS
b. 60 ml 10% D +40 ml NS
c. 60 ml NS + 40 ml 10%D
d. 20 ml NS + 80 ml 10% D

20 ml 10% D + 80 ml NS

**10 ml 10% D + 90 ml NS**

**81. Drug causing hemorrhagic cystitis :**
a. Prilocaine
b. Cyclophosphamide
c. Vincristicine

**Cyclophosphamide**

**82. A lady cosnumes a drug for repeated vomiting during pregnancy. Baby was born with seal like deformity. Drug taken was :**
a. Thalidomide
b. Tetracycline

**Thalidomide**

S/e : neurotoxic – peripheral neuropathy
Teratogenic : phacomelia = seal like limbs
Uses :

| | |
|---|---|
| Inhibit TNF alpha | ENL |
| Antiinflammaotry | MM (with steroids)<br>Actinic prurigo<br>Chronic bullous dermatosis of childhood |
| Inhibits angiogenesis | Macular degeneration<br>Kaposis' sarcoma<br>Aphthous ulcers |

**83. What will happen if EDTA is given along with carbonic anhydrase:**
a. EDTA will chelate metal ion which act as a cofactor
b. EDTA & Ca will form an inactive compund

**EDTA will chelate metal ion which act as a cofactor**

## PSM

**84. Maximum association with heart disease**
a. LDL
b. HDL
c. VLDL
d. Chylomicorns

**LDL**

**85. There is an outbreak of MRSA infection in ward. What is the best way to control it :**
a. Empirical vancomycin to all patients
b. Frequent ward fumigation
c. Hand washing before and after attending patients
d. Wearing masks before any invasive procedure in ICU

Hand washing before and after attending patients

**86. Confounding bias is reduced by a/e :**
a. Matching
b. Blinding
c. Multivariate analysis
d. Randomization

**Multivariate analysis**

| **Eliminate confounding factors** | **Eliminate bias** |
|---|---|
| Randomization (Best)<br>Restriction<br>Matching<br>Stratification | Randomization<br>Blinding |

| | |
|---|---|
| Stastical modeling | |

**87. Hard tick causes All except:**
a. Relapsing fever
b. KFD
c. Indian tick typhus
d. Tularemia

**Relapsing fever**

Hard tick transmitted ds:
1. Tick typhus = rocky mountain spotted fever
2. Viral encephalitis = Russian spring summer
3. Viral fever = Colorado tick fever
4. Viral hemorrhagic fever = KFD (also by soft tick)
5. Tularemia
6. Tick paralysis
7. Human babesiosis

**88. A person wants to study disease X and fat consumption. He obtained data for number of people affected with X from government and details of fat consumption from food industry, type of study :**
a. Ecological
b. Cross sectional
c. Pesiological
d. Experimental

**Ecological**

**89. Calculate NMR fromfollwoing data : total births in a year 4050 – still birth 50 – death within first 7 days 50 – deaths within 7-28 days 150 :**
a. 12.5
b. 50
c. 62.5
d. 49.4

**50**

**NMR = death within 28 days/ total live births x 1000**
**= 150 +50 (7days + 7-28days) / 4050-50 (TB-SB) x 1000**
**= 200/4000x1000 = 50**

**90. A study revealed in some group Beta carotene intake decreases Ca colon , some other study revealed increased intake of dietary fibers decrease Ca colon and nondietary fibers increases Ca colon this is due to :**
a. Confounding factor
b. Mis classification
c. Cohort study
d. Experimental study

**Confounding factor**

**91. Small pox eradication was successful because of all except :**
a. Subclinical cases don't transmit disease
b. Highly effective vaccine
c. Lifelong immunity
d. Cross resistance with animal pox

**Cross resistance with animal pox**

**Small pox was eradicated due to :**
1. No known animal reservoir
2. No longterm carrier
3. Life long immunity
4. Simple case detection by characteristic rash
5. Subclinical cases do not transmit disease
6. Highly effective vaccine – easily administered – heat stable – long term protection
7. International cooperation

**92. Mass prophylaxis is given for all except :**
a. Lymphatic filariasis
b. Vit A deficiency
c. Scabies
d. Worm infestation

**Scabies**

**Medicine**

**93. 60 yr female – 8 transufsions in 2 years – Hb 6 – TC 5800 – Platelet 3.4 lakhs – MCV 60 – RBC 2.1 lakhs /cu mm – p.s. microcytic & normocytic . which Ix is not needed ?**
a. Urine hemosiderin
b. Pulmonary hemosiderosis evaluation
c. BM examination
d. GI scopy

**Urine hemosiderin**

**Microcytic anemia**
- BM examination : hypoproliferative anemias & iron def
- GI scopy : for chronic blood loss / malabsorption : iron def
- 8 transfusion in 2 yr : signs of overlaod occurs after 100 units of RBC (20g total body iron) – while here it is 8x250 mg (iron in 1 unit RBC) = 20 g : so evaluation for endocrine , hepatic , cardiac and pulmonary hemosiderosis

is need
- Urine hemosiderin : hemolytic and Macrocytic anemia

**94. Not used in treatment of hyperkalemia without ECG changes:**
a. Glucose + insulin infusion
b. Calcium gluconate
c. Sodium bicarbonate
d. Salbutamol

**Calcium gluconate**

**95. Find the wrong match:**
a. LKM1 : chronic hepatitis C
b. LKM2 : drug induced hepatitis
c. LKM2 : chronic hepatitis D
d. LKM1 : autoimmune hepatitis

LKM2 : chronic hepatitis D

**LKM = liver kidney microsome**
- **LKM-1 : autoimmune hepatitis type2 & chronic HCV**
- **LKM-2 : drug induced hepatitis**
- **LKM-3 : chronic hepatitis D**

Autoimmune hepatitis
ANA positive
- Type1 : pANCA & Ab to actin

ANA negative
- Type 2 : LKM-1 (anti cytP4502d6) & anti liver cytosolic formaminotransferase (anti liver cytosol-1)

ANA & LKM-1 negative
- Type 3 : Ab to soluble liver antigen (SLA)/liver pancreas antigen

**96. Not correct reagarding treatment of hepatitis B :**
a. Acute : supportive Rx
b. Chronic : supportive Rx
c. Acute : antiviral drugs
d. Chronic : antiviral drugs

**Acute : antiviral drugs**

**HBV**

| Acute | Chronic |
|---|---|
| **Supportive Rx** only (rarely require antiviral treatment with lamivudine in severe case) | **Supportive Rx** **Antiviral drugs :** IFN alpha / PEG IFN alpha/ lamivudine/ adefovir/entecavir |

Treatment :
- Chronic HBV – IFN alpha / PEG IFN alpha/ lamivudine/ adefovir/entecavir
- Chronic HCV – PEG IFN alpha + ribavarin
- Chronic HDV – IFN alpha/PEG IFN alpha
- Autoimmune & cryptogenic hepatitis – prednisone/azathioprine
- Drug induced – withdraw drug

| liver disease | HBe Ag positive | HBe Ag negative |
|---|---|---|
| **Mild/inactive clinically (don't undergo liver bx)** | No treatment – monitor | No treatment : inactive carrier |
| **Chronic hepatitis with normal ALT (<2 UNL)** | No treatment or Do liver Bx → if abnormal → treat | Do liver Bx → if abnormal → treat |
| **Chronic hepatitis with elevated ALT (>2 UNL)** | Treat with : PEG IFN weekly s.c. for 1 year or oral drugs (lamivudine/adefovir/entacavir) for 1 yr (or 6 months after HbeAg seroconversion) IF refractory / immunocompromised patient : use oral drugs (lamivudine/adefovir/entacavir) | As HbeAg seroconversion is not an option goal of treatment is to suppress HBV DNA and maintain normal ALT Lamivudine is resistant : adefovir/entacavir can be used PEG IFN weekly s.c. inj. For 1 yr is preferred |
| **Compensated cirrhosis** | Observe if DNA is $<10^4$ copies | |

| | |
|---|---|
| | if $>10^4$ copies : treat withoral drugs (lamivudine/adefovir/entacavir) not by PEG IFN |
| **Decompensated cirrhosis** | oral drugs (lamivudine/adefovir/entacavir) not by PEG IFN<br>refer for liver transplant |

**97. 30 yr male patient with thunderclap headache , ptosis of right eye. Probable diagnosis :**

a. Aneurismal SAH
b. Stroke
c. Basilar migraine
d. Cluster headache

**Aneurismal SAH**

**98. Loudness of murmur increases on vlasalva maneuver in :**

a. HOCM
b. MS
c. AS
d. VSD

**HOCM**

**99. Prolonged PT & APTT has defect in :**

a. Intrinsic pathway
b. Extrinsic pathway
c. Common pathway
d. Platelet disorder

**Common pathway**

**100. 25 yr male with chronic renal ds with renal failure. His maternal uncle died due to same disease at 28 yrs of age. Slit lamp examination shows keratoconus. Diagnosis is :**

a. ADKPD
b. ARKPD
c. Alport' syndrome
d. Deny drash syndrome

**Alport syndrome**

**101. All are channelopathies except :**

a. Cystic fibrosis
b. Periodic paralysis
c. Liddle syndrome
d. Tay sach's disease

**Tay sach's disease**

**102. DM can be diagnosed by all except :**

a. GTT
b. Fasting glucose
c. D-xylose
d. RBS

**D-xylose**

**Criteria for DM diagnosis :**

- Symptomps + RBS 11.1 mmol/L (200 mg/dl) or
- FBS (8 hr fasting) 7 mmol/L (126 mg/dl) or
- 2 hr plasma glucose 11.1 mmol/L (200 mg/dl) during 75 gm oral GTT

**103. 10 yr old boy – short stature – polyuria and polydypsia – ph 7.34- CO2 32 mm Hg – HCO3 16 – Na 140 – K 4.9 – Cl 112**

a. Anion gap metabolic acidosis
b. Non anion gap metablic acidosis
c. Metabolic alkalosis
d. Chronic respiratory acidosis

**Non anion gap acidosis**

**Anion gap= 140 – (112 +16) = 12**

**104. Not a minor criteria in Multiple myeloma :**

a. Plasma cells 20%
b. Plasmacytoma on tissue biopsy
c. Multiple lytic bone lesions
d. IgA 2.5 g/dl ; IgG 3.5 g/dl

**Plasmacytoma on tissue biopsy** > IgA 2.5 g/dl ; IgG 3.5 g/dl

**MM**

**At least 1 major criteria :**

1. **Plasmacytoma on tissue biopsy**
2. BM with 30% plasma cells
3. **M protein spike on electrophoresis**
   a. **Ig G > 3.5 g/dl**
   b. **Ig A > 2 g/dl**
4. Bence jones light chain proteinuria >1g/d

**Atleast 1 minor criteria**:

1. **BM plasmacytosis 10-30%**
2. **M proteinspikeon electrophoresis**
   a. **Ig G < 3.5 g/dl**

**b. Ig A < 2 g/dl**
**3. Lytic bone lesions**
4. Decreased residualimmunoglobulins

**105. Splenomegaly is least likely in :**
a. PCV
b. CML
c. Primary thrombocytosis
d. Primary myelofibrosis

**Primary thrombocytosis**

**106. Inclusion body in oligodendrocyte are characteristic of**
a. Japanese encephalitis
b. CJD
c. PML
d. Polio

**PML**

- JC virus : inclusion bodies in oligodendrocytes
- Causes Progressive multifocal leucoencephalopathy
- Associated with brain tumors like medulloblastoma

**107. Horner's syndrome is seen in all except :**
a. Medial medullary syndrome
b. Multiple sclerosis
c. Carotid artery aneurysms
d. As a result of treating Raynaud's phenomenon

**Medial medullary syndrome**

**108. Caison's disease is due to :**
a. Gas embolism
b. Fat embolism
c. Amniotic fluid embolism
d. Tumor embolism

**Gas embolism**

**109. Congential cause of hypercoagulable state are all except:**
a. Protein C deficiency
b. Protein S deficiency
c. Mutation of MTHFR
d. Antiphospholipid Antibody syndrome

**Antiphospholipid Antibody syndrome :** It is an acquired hypercoaguable state not congenital

- Mutation in MTHFR : methylene tetra hydro folate reductase → homocystenemia (atherogenic and thromboembolic)
- Homocystenemia & deficiency of folate & B12 are associated with increased risk of NTD in pregnant women
- Protein C & S deficiency : cause DVT & pulmonary embolism- Also associated with warfarin induced skin necrosis over central areas of body (breast , abdomen and genitalia)

**110. A 30 years old female was posted for surgery. APTT is prolonged with normal PT. 2 years back she was operated for cholecystectomy , but she didn't have any bleeding . next investigation for clinical diagnosis ?**
a. Factor VIIIc assay
b. Russel viper venom titre
c. Platelet aggregation tests
d. Ristocetin cofactor assay

**Russel viper venom test :** lupus anticoagulant (positive) can be differentiated from acquired inhibitors (negative test)

- Factor VIIIc assay: hemophilia may present with isolated prolonged APTT but no bleeding during previous surgery , so ruled out
- Platelet aggregation tests : don't cause prolonged APTT
- Ristocetin cofactor assay : VWD can cause prolonged APTT but no bleeding during previous surgery so ruled out

**111. A 75 yr female with fracture neck femur 1 month back presents with 2 days h/o of altered sensorium , decreased urine output ,urea 140 mg/dl , creatinine 2 mg/dl , Calcium 15.2 mg/dl . all are useful in immediate treatment except :**
a. Hemodialysis
b. Give NS
c. Bisphosphonate
d. Furosemide

**Bisphoshonate**

Hypercalcemia :
Treatment :
Bisphosphonate can be used in treatment but they are C/I in renal dysfunction and esophageal motility disodrders

**Surgery**

**112. Perineural invasion is commonly seen in :**
a. Adeno Carcinoma
b. Adenoid cystic Carcinoma
c. Basal Cell carcinoma
d. Squamous cell Carcinom

Adenoid cystic Carcinoma

**113. Brilliantly transillumination seen in all except :**

**Lipoma**

a. Cystic hygroma
b. Vaginal hydrocele in infant
c. Spinal meningocele
d. Lipoma

**114. Not true about charcot's triad :** **Palpable gall bladder**

a. Pain
b. Jaundice
c. Fever
d. Palpable Gall bladder

**115. 20 yr old man with bilious vomiting no physical significant findings . barium follow through will clinch diagnosis . The procedure done Ladd's band lysis , widening of base of mesentery and appendecectomy . likely diagnosis :** **Malrotation**

a. Malrotation
b. Tuberculous stricture
c. Recurrent cecal volvulus
d. Recurrent appendicitis

**116. Most resistant to lithotripsy :** **Cysteine**

a. Calcium oxalate
b. Triple phosphate
c. Uric acid
d. Cysteine

**117. Cock's peculiar tumor is :** **Ulcerated Sebaceous cyst**

a. Ulcerated sebaceous cyst
b. Squamous cell Ca
c. Cylindroma
d. Basal Cell Ca

**118. A 45 year old business man who travels frequently. He c/o fresh bleeding while defecation since 7 days. P/R normal.no other symptomps. CXR normal . P/A normal. As a General practitioner what will you do?** **Proctoscopy**

a. Proctoscopy
b. Do barium enema
c. Refer to surgeon for sigmoidoscopy
d. Refer a gastroenterologist for colonoscopy

Mc cause of lower GI bleed : hemorrhoids : P/R may be normal →next : proctoscopy → if normal → sigmoidoscopy / colonoscopy by gastroeneterologist

Barium enema is useful only in massive LGI bleed as in diverticulosis

**119. Fogarty catheter is used for :** **Intraarterial embolectomy**

a. Bladder drainage
b. Ureteric catheterization
c. To give Parenteral nutrition
d. Intraarterial embolectomy

**120. A patient with recurrent renal stone since 2 years all advises are given except :** **Calcium restriction**

a. Plenty of fluids
b. Salt restricted diet
c. Protein restricted diet
d. Calcium restriction

- Restriction of calcium will increase oxalate absorption
- Increase fluid intake leads to dilute urine :decrease stone formation.
- High protein & sodium increase risk calcium oxalate & uric acid stones
- Citric acid (highest lemon juice) & dietary fibers reduces risk.

**121. Which is false ?**

a. Raccoon eye is due to subglaeal hemorrhage
b. Carotico cavernous fistula occur in base skull fracture
c. Post traumatic epilepsy occurs in 15% cases
d. Depressed skull fracture is associated with more brain injury

Post traumatic epilepsy occurs in 15% cases

Base of skull fractures

- Associated $7^{th}$ /$8^{th}$ nerve palsy
- CSF leaks :
  - # temporal bone
    - → SA space → middle ear → ear/pharynx via E.tube (CSF otorrhea
    - Echymosis behind ear =battle's sign
  - # anterior base

- Anosmia : olfactory nerve damage
- CSF rhinorrhea
- **Periorbital echymoses : Racoon eyes**

**122. Organism associated with infected fish consumption and causation of gall bladder cancer :**

a. Gnathostoma
b. Clonorichis cinensis
c. Strongyloides
d. Ankylosotma duodenale

**C.cinensis**

**123. In follow up of BPH patient most important indication of doing TURP is**

a. Prostate size >75 gm
b. UTI episode requiring 3 days antibiotics
c. B/L hydroureteronephrosis
d. Hypertensive patient not tolerating alpha blocker

B/L hydroureteronephrosis

**124. A 65 yr male with enlarged prostate and B/L hydrouretero nephrosis. Prostate 70 gm. Residual urine volume is 400 ml . urea 140 mg , creatinine 3.5. immediate treatment is :**

a. Foley's catheter
b. B/L percutaneous nephrosotmy
c. Suspect prostatic Ca & do CECT
d. MRI pevis

**Foleys catheter**

- Patient is in renal failure due to BOO (by BPH/Ca prostate) → do foley's catheterization → fails → suprapubic cystostomy
- In case of suspected Ca prostate → do Trans rectal USG and biopsy (CT & MRI are used for staging not for treatment)

## Pediatrics

**125. A new born with RR 86/min – marked flaring of nasal ala – grunting – lagging of abdomen than chest (lower chest retractions) – silver man scoring is**

a. 1
b. 3
c. 4
d. 6

**6**

**Respiratory distress syndrome**

**Silverman-Anderson scoring system (not include RR)**

| Score | 0 | 1 | 2 |
|---|---|---|---|
| **Upper chest retractions** | Synchronized | Lag on inspiration | See saw movement |
| **Lower chest retractions** | None | Just visible | Marked |
| **Xiphoid retractions** | None | Just visible | Marked |
| **Nasal flaring** | None | Minimal | Marked |
| **Expiratory grunting** | None | With stetho only | Naked eye and ear |

**Downe's scoring system**

| | | | |
|---|---|---|---|
| **Cyanosis** | None | In room air | In 40% FIO2 |
| **Retractions** | None | Mild | Severe |
| **Grunting** | None | With stetho | Ear |
| **Air entry** | Clear | Decreased | Barely audible |
| **RR** | <60 | 60-80 | >80/apnea |

**Score**
**>4 = clinical respiratory distress →monitor ABG**
**>8 = impending respiratory failure**

**126. A newborn after 6 hrs of birth crying lustily with closed eyes , moving all 4 limbs , neonatal behavioral scale is :**

a. 1
b. 2
c. 3
d. 4

**5 > 4**

Alertness of newborn is assessed by Prechtel & Beintema scale

| Stage | Eyes | Respiration | Movements |
|---|---|---|---|
| **1** | Closed | Regular | No |
| **2** | Closed | Irregular | No |

| | | | |
|---|---|---|---|
| **3** | Open | - | No |
| **4** | Open | - | Yes |
| **5** | Open/close | Crying | Yes |

**Neurological examination is best done in stage 3**

**127. A newborn child developed respiratory depression in ward. Following drug may be the cause**

a. Opioids
b. Barbiturates
c. Diazepam
d. Propofol

**Opioids**

**128. 7 yr male child with +1 proteinuria – 15 to 20 pus cells – 1-2 RBCs – BP 180/110 – no previous significant past history :**

a. Postinfectious GN
b. Idiopathic RPGN
c. Accelerated HT with ARF
d. Chronic interstitial nephritis with VUR

**Chronic interstitial nephritis with VUR** > post infectious GN

**129. A 30 week gestation mother delivered 1.2 kg baby with moderate respiratory distress. RR 70/min- grunting – chest retractions – most logical next step is :**

a. Warm humidified oxygen via hood
b. Nasal CPAP
c. Surfactant and mechanical ventilation
d. Mechanical ventilation

**Surfactant and MV**

**130. A 10 year old male child c/o pain in left hypochondrium since 2 days.Hb 9.69% . his mother gives h/o passing black colored stools since 7 days and on 2-3 occasions since 2 years. During these episodes he had fatiguability while playing and was not able to play with his peers. Which of the following will maximally help to arrive at clinical diagnosis ?**

a. Pallor
b. Jaundice
c. Palpable spleen
d. Free fluid in abdomen

**Palpable spleen**

- Pain in LHC = splenic enlargement
- Malena + anemia = upper GI bleed= varices
- Mc cause of portal HT in children = EHPO
- Bleeding is since 2 years = patient is well tolerated - may or may not manifest with hemetemesis : extrahepatic Portal HT
- Severe bleeding and acute progressive presentation : hepatic portal HT
- Palpable spleen suggest EHPO

**131. Calculate ponderal index of a child with 2000 g and height 50 cm :**

a. 1.6
b. 3.6
c. 2.2
d. 2.6

**1.6**

**Ponderal index =weight (g) x 100/ height (cm)$^3$**

**132. A preterm baby with PDA , least likely finding is :**

a. CO2 washout
b. Bounding pulses
c. Pulmonary hemorrhage
d. Necrotising enterocolitis

**CO2 washout**

- PDA – hyperdynamic state – bounding pulse – wide pulse pressure
- Tachypnea/apnea – CO2 retention – require mechanical ventilation
- High PBF – pulmonary hemorrhage
- Preterm infants – PDA is common – hemodynamic stress – risk factor for NEC

**133. Indicates ABO incompatibility in newborn :**

a. Microspehrocyte
b. Fragmented RBCs
c. Polychromasia
d. Elliptocytosis

**Microspherocyte**

- Microspherocytosis : HS /AIHA/ ABO incompatibility / thermal injry/ clostridial septicemia / wilson's disease
- Fragmented RBCs : microangipathic HA
- Polychromasia : premature RBC =reticulocyte
- Elliptocytosis : hereditary elliptocytosis

**134. A child with microcytic hypochromic anemia with Hb40 g/L – S.iron 20 mcg – S ferritin 600 ng/ml – S.transferin ?**

**saturation 64% - diagnosis is :**

a. IDA
b. Hemochromatosis
c. Atransferinemia
d. DMT 1 mutation

**Here High Hb – low S.iron (N-50-150 mcg/dl) – very high S.ferritin (N- 50-200 mcg/L) – very high transferin saturation (N – 30-50%)**

| | IDA | Hemochromatosis | Atrasferinemia | DMT-1 |
|---|---|---|---|---|
| Hb | Low | High | High | High |
| S.iron | Low | High | High | High |
| s.ferrtiin | Low | High | Very High | high |
| % sat | Low | High | Very low/absent | Very high |

**135. Which of the following favours diagnosis of RDS in newborn ?**

a. Antenatal steroids
b. Air bronchogram on CXR
c. Manifest after 6 hrs
d. Occurs after term gestation

**Air bronchogram on CXR**

- Antenatal steroids : prevent RDS
- Air bronchogram on CXR : suggestive of RDS
- Manifest after 6 hrs : RDS manifest immediately after birth
- Occurs after term gestation : occurs in preterm and rarely in term babies with genetic causes (protein B& C mutation/ABCA3 mutation)

**136. Not a major criteria of Jones in rheumatic fever ?**

a. Pancarditis
b. Arthritis
c. Chorea
d. High ESR

**High ESR**

Modified jones criteria :

| **Essential : evidence of recent strep infection**<br>High/rising ASO / positive throat culture /rapid Ag forgr.A strep / recent scarlet fever | |
|---|---|
| **Major** | **Minor** |
| • **Migratory polyarthritis**<br>• **Carditis**<br>• S.c. painless nodules<br>• erythema marginatum<br>• **Sydenham's chorea** (st. vitus' dance) | Fever<br>Arthralgia<br>**High ESR**/WBC<br>ECG : long PR (heart block) |

**137. Least likely cause of neonatal mortality in India :**

a. Severe infections
b. Congenital malformations
c. Prematurity
d. Birth asphyxia

**Congenital malformation**

Neonatal mortality causes in descending order:

1. **Prematurity**
2. **Sepsis**
3. **Asphyxia at birth**
4. **Congenital anomalies**
5. Neonatal tetanus
6. Diarrhea

**138. Test done to differentiate fetal and maternal blood :**

a. Kleihauer betke test
b. Apt test

?

Kleihauer betke test : quantitative test (MC done)
Apt test : qualitative test

**139. Which of the following is associated with maternal disomy of chromosome 15 ?**

a. Prader willy syndrome
b. Angelman syndrome
c. Hydatiform mole
d. KFS

**Prader willy syndrome**

| **Prader willy syndrome** | Angelman syndrome |
|---|---|
| **Maternal UPD** (uniparental disomy ) Ch 15 : 2 maternal and **no paternal chromosome** | Paternal UPD (uniparental disomy) Ch 15: 2 paternal and no maternal chromosome |
| **Paternal deletion Ch15q** > maternal deletions > imprinting mutations | Maternal deletions > imprinting mutations > mutation in UBE3A gene (only maternaly imprinted gene on Ch15) > paternal deletions |
| Obesity, hypogonadism, mental retardation | Ataxic gait |

The **UPD** cases are mostly caused by meiotic nondisjunction

resulting in trisomy 15, subsequently followed by a normalizing mitotic nondisjunction event ("trisomy rescue") resulting in two normal chromosomes 15, both from the same parent

**Genomic imprinting** = differential expression of certain genes on different chromosomes

Chromosome 11 : **Beckwith-Wiedemann** overgrowth syndrome : have **two paternal but no maternal** copies of this chromosome : **maternal UPD ch 11**

**140. True about HMD is :**

a. FRC > closing volume
b. FRC < closing volume
c. FRC = Closing volume
d. FRC is indepenedent of closing volume

**FRC < closing volume**

**Closing volume =** volume of lung above which dynamic compression and closure of airway begins
Once airway closes gases cannot reach/come out of alveoli
Closing capacity = Closing volume (CV) + residual volume (RV)
Residual volume = volume remaining in lung at end of forced expiration
CC is more in infants due to low recoil of lung : hence preterm breathe from end expiratory lung volume which is close to CC
Large CV – increase dead space ventilation → atlectasis and shunting
Elastic tissue keep airway open – lower lung volume required before gravitational forces can close small noncartilagenous airways
FRC = lung volume at end expiration
FRC is low in collapse / surfactant deficiency

**HMD – surfactant deficiency → FRC is low (FRC <CC) → collapse of lung → increase v/q mismatch**
**Aim of CPAP : Increase FRC (FRC>CC)**

**141. New born babies are able to breathe and suck at same time due to :**

a. Wide short tongue
b. Short soft palate
c. High larynx
d. Short pharynx

**High larynx**

**At birth larynx is high in neck → placing epiglottis in close contact with soft palate → allows infant to breathe through nose while sucking and swallowing**

**O & G**

**142. Not used as emergency contraceptive :**

a. LNG IUD
b. Oral LNG
c. Oral mifepristone
d. Cu T

**Oral mifepristone**

| | | |
|---|---|---|
| Within 72 hours of coitus : | | |
| High dose estrogen<br>Ethinyl estradiol (EE)<br>Conjugated equine estrogen<br>(CEE)<br>(not in use now) | <br>2.5mg BD x 5d<br>15 mg BD x 5d | FR<br>0.15%<br>0-0.6% |
| **Combined E+P** | | |
| **Yuzpe** : Overal<br>EE 50 microgm +<br>LNG 0.5 mg | 2 tab stat → 2 tab after 12 hrs<br>(total dose : EE 0.2 mg & LNG 2 mg) | 0-2% |
| **Low dose pills :**<br>(overall-L , Mala-N)<br>EE 30 microgm +<br>LNG 0.15 mg | 4 tab stat → 4 tab after 12 hrs | 0-2% |
| Within 72 hours upto 5 days | | |
| **LNG**<br>(Ecce-2 /i-pill/E- | 0.75 mg stat →<br>0.75mg after 12 hrs | 0-1% |

| | | |
|---|---|---|
| pill/unwanted 72 / paln-B) | Or<br>1.5 mg stat | |
| **Centchroman 30 mg (saheli)** | 2 tab BD x 1d | Not known |
| **Danazole** | 400/800 mg BDx3d<br>Or<br>1200 mg BD x 2d | 0.8-1.7% |
| Within 7 days | | |
| **Copper IUD (more effective than steroids)** | | <1% |
| **Within 5 days to 27 days of menstrual cycle** | | |
| **Mifepristone (RU-486)** | 600/200/10 mg SD | 1.3% |

**All are used : but mifepristone has higher complication rate so not used commonly**

**143. Clue cells are seen in**
a. Bacterial vaginosis
b. Candidiasis
c. Chlamydiasis
d. Trichomoniasis

**Bacterial vaginosis**

**Bacterial vaginosis :**

*Amsel* criteria for diagnosis of bacterial vaginosis:
1. White homogenous vaginal discharge
2. Ph > 4.5
3. Fishy odor (volatile trimethylamine)on mixing with 10% KOH = whiff test
4. **Clue cells**

**Clue cells :** vaginal epithelial cells – coated with coccobacillary organisms –granular appearance- indistinct borders – seen on normal saline mount

**144. Urine of 3rd trimester pregnant women will shoe presence of :**
a. Glucose
b. Fructose
c. Galactose
d. Sucrose

**Glucose**

**145. Regimen used for expectant management of placenta previa**
a. Macaffe & Jhonson
b. Braude Andrene
c. Credes
d. Liley's

**Macaffe & Jhonson**

Bed rest + tocolysis + close observation + steroids
Atleast 3 criteria should be fulfilled before following it :
1. HD stable mother
2. No fetal distress
3. Pregnancy < 36 weeks

**146. Patient is in shock after normal labour . Most likely cause is :**
a. Uterine inversion
b. PPH
c. Amniotic fluid embolism
d. Eclampsia

**PPH**

**147. A patient with Ca cervix stage IIIb , TOC**
a. CT
b. Intracavitary brachytherapy → external beam RT
c. Werthiem's s hysterectomy
d. Schauta's operation

Intracavitary brachytherapy → external beam RT

Management of Ca cervix :

| Stage | | |
|---|---|---|
| I | Confined to cervix | |
| Ia | Microscopically | |
| Ia1 | ≤3 mm deep<br><7 mm wide | Conization /<br>type 1 H |
| | ≤3 mm deep<br>+ LVSI | Radical trachelectomy /<br>type 2 H |
| Ia2 | >3-5 mm<br><7 mm wide | |

| | | |
|---|---|---|
| Ib | Visible with naked eye | |
| Ib1 | >5mm invasion ,size <2 cm | Radical trachelectomy / type 3 H |
| | >5mm invasion ,size >2cm <4cm | Type 3H |
| Ib2 | >4cm | Type 3H + paraaortic LN / Primary chemoradiation |
| IIa | No parametrium | |
| IIb | Parametrium | Primary chemoradiation |
| IIIa | Lower 3rd vagina | |
| IIIb | Pelvic wall Hydronephrosis | |
| Iva | Bladder Rectum | Primary chemoradiation/ Primary exentration |
| IVb | Distant organs | Primary chemotherapy ± RT |

**1A2,1B,IIA : radical/wertheim's hysterectomy**
**IIB-IV : Radiotherapy (cisplatin given before ) = chemoradiation**

**148. All are risk factors for vaginal candidosis except :**
a. DM
b. Pregnancy
c. HT
d. HIV

**HT**

**149. Endomtrrial Ca involving >50% of myometrium , vagina , no metastasis , no pelvic /paraaortic LN , parametrial cytology + . stage is :**
a. IIIa
b. IIIb
c. IIIc1
d. IIIc2

**IIIb**

FIGO staging :

| | |
|---|---|
| Ia | No myometrial invasion |
| Ib | <50% myometrial invasion |
| Ic | >50% myometrial invasion |
| IIa | Endocervical glands |
| IIb | Cervical stroma |
| IIIa | + uterine serosa , adnexa and/or peritoneal cytology |
| **IIIb** | **Vagina** |
| IIIc | Pelvic / paraaortic LN |
| Iva | Bladder/bowel mucosa |
| Ivb | Distant metastasis Inguinal LN |

**150. Prolonged administration of testosterone in male leads to :**
a. High GnRH
b. Increased spermiogenesis
c. Azoospermia
d. High sperm motility

**Azoospermia**

**151. Most appropriate treatment for eclampsia:**
a. MgSO4
b. Lytic cocktail
c. Phenytoin
d. Diazepam

**MgSO4**

**152. If mother received lithium for BPD. Fetus is likely to show :**
a. NTD
b. Facial defects
c. Urogential anomaly
d. Cardiac anomaly

**Cardiac anomaly**

| | |
|---|---|
| **Phenytoin** | **Fetal hydantoin syndrome** |
| **Valproate** | **Spina bifida (1-2%)** |
| **Warfarin** | **Chondrodysplasia punctata** |

**153. 20 yr female with excess facial hair , oligomenorrhea ,**

**Testosterone secreting tumor**

**high free testosterone , normal ovaries on USG . female weight was average. Most likely diagnosis :**

a. PCOD
b. Adrenal hyperplasia
c. Idiopathic hirsuitism
d. Testosterone secreting tumor

**PCOD :**

- diagnostic criteria
  - Oligomenorrhea
  - Hyperandrogenemia : clinical/serological evidence
  - USG : 9-10 mm **multiple small follicles in ovary and enlarged ovary**
- **Obesity** – HT – DM usually associated
- Lean patients have high LH in presence of normal to Low FSH and estradiol

**154. A patient with primary amenorrhea – normal breast and pubic hair – absent uterus and vagina . diagnosis is :**

a. Mullerian agenesis
b. KFS
c. Gonadal dysgenesis
d. 46 XYY

**Mullerian agenesis**

**Mullerian agenesis = Mayer Rokitanski Kuster hauser syndrome**

- (46) XX – ovaries – no androgen (or female levels) – wolfian regresses
- Mullerian agenesis – **no uterus :primary amenorrhea**
- **Breast developed**
- **Axillary & pubic hair** (differentiate it from AIS)
- Sporadic inheritance

| | **Uterus FT Vagina** | **Breast** | **Pubic & axillary hair** |
|---|---|---|---|
| pure gonadal dysgnesis (sweyer) | Normal | Absent | |
| Mixed gonadal dysgenesis | Normal | Absent | |
| Turner | Under developed | Under developed /absent | |
| **MRKS** | **Absent** | **Normal** | **Normal** |
| AIS | Absent | Normal | Scanty/ absent |

**155. A 32 yr women at 9 weeks gestation has a son of 10 yrs age with downs syndrome . she doesn't want another child with downs . what would you advice her?**

a. Maternal blood examination can diagnose down's at this time of pregnancy
b. USG can diagnose at this time of pregnancy
c. Can do CVS to definitely diagnose down's
d. No need to do any investigations as there is minimal risk since her age is < 35 yrs

Can do CVS to definitely diagnose down's

- As there is past history of downs→ do a confirmatory test
- Triple marker is a screening test
- USG can be normal in downs
- To confirm down's – do karyotyping – sample obtained by CVS/amniocentecis
- Amniocentesis is done at 14-18 weeks

| **Transabdominal CVS** | Transcervical CVS |
|---|---|
| Done at **10 weeks-term** | Done at 10-12 weeks |
| Done if placenta in in upper 2/3rd of uterus | Done if placenta is in lower 1/3rd of uterus |
| More commonly doen (80%) | In 20% cases only |
| Advantages :<br>1. Can be done in 2nd and 3rd trimesters<br>2. No vaginal bleeding<br>3. Minimal risk of infection | Advantages :<br>1. Genetic diagnosis at early gestational<br>2. No pain to patient<br>3. Simple technique |
| Disadvantages : | Disadvantage: |

| | |
|---|---|
| 1. Pain is more<br>2. Difficult technique<br>3. Less tissue is obtained | 1. Fetal loss 0.8% more than amniocentesis<br>2. Chromosome/enzyme compostion of chorionic villus may be different from fetal cells<br>3. C/I in some conditions |

**156. Corpus cancer syndrome includes all except :**

a. HT
b. DM
c. Multiparity
d. Obesity

**Multiparity**

**Endometrial Ca = corpus cancer**
**Risk factors – estrogen dependent tumor**

1. Nulliparous
2. Late menopause
3. Obesity
4. DM
5. HT
6. Unopposed estrogen therapy
7. Tamoxifen
8. Atypical endometrial hyperplasia

**157. A lady with LSCS with BP 150/100 mm Hg at 37 week – on P/v os is closed – cervix soft and posterior 50% effaced – station -3 – pelvis adequate- best treatment**

a. Induction labor
b. CS
c. vaginaldelivery
d. Rest + antiHT + wait for normal labor

**CS**

- In PIH pregnancy should be terminated at or after 37 weeks even if BP is normal : cannot wait for normal labour
- As previously LSCS has been done – induction of labor /vaginal delivery is C/I : CS is preferred
- If previosusly LSCS not done : induction of labor

**158. Classification of abruption placenta**

a. Macaffee
b. Jhonson
c. Page
d. Apt

**Page's classification for abruption placenta:**

Grade:
0: retrospective diagnosis after delivery
1: external bleed / tender uterus/ no fetal distress
2 : fetal distress/IUD
3: maternal shock ± DIC

**159. Natural ovulation cycle is mostly on right side. It is least likely due to**

a. Anatomical difference b/w 2 ovaries
b. Right handedness
c. Vascular supply
d. Embryogenesis

**Right handedness**

**ENT**

**160. True about cochlear implant :**

a. c/I in <5year old
b. can be placed through oval window
c. not c/I in cochlear malformations
d. useful in mild to moderate hearing loss

**Not C/I in cochlear malformations**
Cochlear implants

- can be done 1 year onwards
- placed through round window
- indications:
  - mild-moderate hearing loss (70 db or worse) with SDS 60%
  - cochlear malformations
  - labyrinthitis ossificans
  - mild cochlear dysplasia : mondini deformity
- contraindications:
  - severe hearing loss

**161. initial management for CSF rhinorrhea :**

a. Craniotomy
b. Close nostril with sterile petrollium jelly pack
c. Frequent blowing of nose
d. Wait for 7-10 days with antibiotic

Wait for 7-10 days with antibiotic

- Craniotomy done only for chronic case (not as initial Mx)
- Never infect nose with jelly : but drugs reducing CSF productions can be used
- Never blow nose : as it produces more CSF and more leakage
- Antibiotic and observation for 7-10 days resolve acute cases

**162. False about retropharyngeal abcess :**
a. Confined to one side of midline always
b. Lies posterior to prevertebral fascia
c. Causes dysphagia and dyspnea
d. Always palpable with finger in posterior pharyngeal wall

Always palpable with finger in posterior pharyngeal wall

**163. Transnasal endoscopic surgery , all structures can be approached except :**
a. Cerebellum
b. Pituitary
c. Optic nerve
d. Lacrimal sac

**Cerebellum**

**Ophthalmology**

**164. A 25 yr male with sudden painless loss of vision. Ocular and systemic examination is not contributory. Most probable diagnosis :**
a. Retinal detachement
b. Eale's disease
c. Glaucoma
d. Cataract

**Eale's disease**

- Retinal detachement : fundus examination +
- Eale's disease : (recurrent) vitreous hemorrhage (neovasculrization from retina) in young male results in sudden painless vision loss – due to TB protein allergy – B scan is done – Rx : (vascultiis) steroids & AKT → (neovasculrization) laser photocoagulation → (Vitreous hemorrhage & RD) vitrectomy and /or tractioanl detachement Sx
- Glaucoma : painful loss of vision
- Cataract : gradual loss of vision

**165. A 70 year old is diabetic and hypertensive since 10 years. c/o partial U/L vision loss . Fundus examination shows central hemorrhagic spot and fellow eye is normal, cause is :**
a. Retinal tear
b. Optic neuritis
c. Diabetic retinopathy
d. Hypertensive retinopthy

**Retinal tear > DM retinopathy ?**

**166. Treatment of threshold ROP :**
a. Laser photocoagulation
b. Controlled oxygenation
c. Reattachement of retina
d. Antioxidants

**Laser photocoagulation**

**ROP = retinopathy of prematurity**

- **Concentric zones centered on optic disc :**
- **Zone 1** : 2(disc-macula distance)
- **Zone 2 :** edge of zone 1 to nasal orra serata
- **Zone 3 :** residual temporal crescent from edge of zone2
- **Staging of ROP**
  - 1 : abnormal vessels leading upto the demarcation line (parallel to orra serata -more prominent on temporal periphery)
  - 2 : blood vessels enter Demarcation ridge and isolated neovascular popcorn tufts posterior to it
  - 3 : extraretinal fibrovasclar proliferation (demarcation ridge to vitreous)
  - 4 : partial RD
  - 4 a : extrafoveal RD
  - 4b : RD involving fovea
  - 5 : total RD
- Plus disaseas (add plus sign to any stae if present)
  - Failure of pupil to dilate
  - Vitreous haze
  - Gross vascular enlargement of iris
  - Dilation of veins and tortuous arteries
- Threshold disease :
  - 5 contagious clock hours or
  - 8 cumulative hor of extraretinal neovasculrization (satge3) in zone 1 or 2 with plus disease
- Rush disease : seen in stage 1 & not progress through classical stages

- Screening :
  - For babies born before 31 weeks or weighing <1500 g
  - Methods :
    - Indirect ophthalmoscopy
    - Wide field retinal camera (retcam) 120 degree
  - Begin 4-7 weeks post natal age to detect threshold disease
- Treatment :
  - Stage 4a : plana vitrectomy for extrafoveal tractional RD
  - Stage 4b & 5 : not successful treatment
  - Threshold disease : laser photocoagulation of immature retina > cryo

**167. Stocker's line is seenin :**
a. Pinguecula
b. Pterigium
c. Ocular melanosis
d. Congenital epithelial melanosis

**Pterigium**
**Deposition of iron in corneal epithelium anterior to advancing head of pterigium is called stocker's line**

**168. Retinitis pigmentosa is not seen in :**
a. Refsum's disease
b. Hallovernden saptz disease
c. NARP
d. Abetalipoproteinemia

None > Hallovernden saptz disease

**Orthopedics**

**169. Gallow's traction is used for fracture of :**
a. Neck femur
b. Shaft femur
c. Shaft tibia
d. Tibial plateau

**Shaft femur**

| Traction | Condition |
|---|---|
| **Gallow** | **#Shaft femur** |
| Russel | #I/T femur |
| Smith<br>Dunlop | # S/C humerus |
| Agnes hunt | Severe flexion deformity hip |
| 90-90 | Triple deformity knee |
| Well leg | Abduction deformity hip |

**170. MC initial site involved in hematogenous osteomyelitis :**
a. Epiphysis
b. Metaphysis
c. Entry of nutrient artery in diaphysis
d. Diaphysis

**Metaphysic**

| Osteolyelitis | MC site |
|---|---|
| **Hematogenous** | **Metaphysis** |
| Garres | Diaphysis femur |
| Salmonella | Diaphysis > metaphysic |
| Brodie's abcess | Metaphysic upper tibia |

**171. Child with foot curved inwards and dorsum of foot is unable to touch with tibia . diagnosis**
a. Arthrogryposis multiplex
b. CTEV
c. Cerebral palsy
d. Congenital vertical talus

**CTEV**
- **Foot inward = Inversion = varus**
- **Dorsum of foot cannot touch tibia = plantar flexed = equins**

**172. A man can abduct and internally rotate upper limb he can place his hand overlumbosacral region but cannot lift off his hand from back. Diagnosis :**
a. Biceps tendon tear
b. Teres major tear
c. Subscapularis tear
d. Acromioclavicular dislocation

**Subscapularis tear**
**Subscpularis lift off test +**

**173. In reimplantation surgery of limb 1st to be done :**
a. Anastomosis of artery
b. Anastomosis of vein
c. Fixation of bone
d. Anastomosis of nerves

**Fixation of bone**

**174. Poor prognostic factor for Ewing sarcoma :**
a. Young age
b. Raised B-2 microglobulin

**Thrmbocytosis**
**Poor prognostic factors for ewoing's sarcoma :**
1. Distant metastasis

c. Fever
d. Thrombocytosis

2. Large size
3. Fever /anemia/high ESR/LDH/thrombocytosis
4. Old age
5. Male
6. Poor response to neoadjuvant CT
7. Early relapse in 1 year

**175. A 30 yr patient with backache . x ray shows collapse of D12 vertebra with normal disc space . least likely diagnosis is :**

a. Multiple myeloma
b. Metastatic lesion
c. TB spine
d. Osteoporosis

**TB spine**

**Reduction of disc space is earliest sign of wedging vertebra in TB spine**

**176. A person with RTA with left knee injury. Dial test is positive. Diagnosis is :**

a. Medial collateral ligament injury
b. Lateral meniscus injury
c. Medial meniscus injury
d. Posterolateral corner injury

**Posterolateral corner injury**

Dial test = tibial external roatation test

- Test for posterolateral (popliteal) corner instability
- Knee is flexed to 30 degree – tibia is externally rotated on femur
- External rotation is increased on affected side
- Conditions causinf popliteal corner instability
  - LCL laxity/injury
  - Popliteal tendon
  - Psot lateral ligament complex

Tests for collateral ligament

| | |
|---|---|
| **Valgus stress test**<br>**Varus stress test** | **Knee 30 flexion** |
| **Lachman test** | **20 flexion** |
| **Drawer test** | **90 flexion** |
| **Pivot shift test/ jerk test (ACL & Antlat stability)** | |
| **Macintosh test (ACL)** | |
| **Sag sighn (PCL)** | |
| **Reverse pivot shift test (post lat instability) – PCL + arcuate complex [LCL+ Arcuate lig + politeus]** | |

**177. Secondary hyperparathyroidism is not seen in :**

a. Osteoporosis
b. Osteomalacia
c. Rickets
d. CRF

**Osteoporosis**

S.Ca is normal in osteoporosis

**Skin**

**178. All are used for chemopeeling except :**

a. Carboxylic acid
b. Phosphoric acid
c. Kojic acid
d. Trichloroacetic acid

**Phosphoric acid**

- Chemical peeling = controlled chemical burn = for resurfacing skin
- Peeling agents
  - Trichloroacetic acid : Mc used
  - Glycolic acid 50%
  - Jessner's solution (resorcinol salicylic acid , lactic acid , ethanol)
  - Resorcinol 40-50%

| | |
|---|---|
| Very superficial (exfoliation) | 10% TCA<br>50% glycolic acid<br>jessner's solution &<br>resorcinol 40% |
| Superficial (epidermal) | TCA 35-50% |

| | |
|---|---|
| Medium (papillary dermis) | glycoli acid 50% augmented TCA (= TCA 35% + Co2 Or jesner's solution or glycolic acid 70%) |
| Deep (reticular dermis) | Baker Gordon phenol formula (liquid phenol + tap water + liquid soap + croton oil) |

- Indications :
  - Photoaging
  - Actinic keratosis
  - Solar lentigo
  - Acne scars
  - Perioral wrinkling
  - Rhytids (prominent nasolabial folds)
- C/I :
  - Active bacterial infections
  - Fungal infections
  - Facial dermatitis
  - Taking photosensitizing medications
- Complications:
  - Post peeling scarring
  - Pain
  - Herpes simplex infection

**179. A farmer presented with verrucous plaque in foot . likely diagnosis :**

a. Tuberculous verruca cutis
b. Mycetome
c. Verruca vulgaris
d. Lichen planus verrucuas

**TB verruca cutis**

- Exogenous source → skin inoculation of TB (abrasive contact with earth/expetctorated bacilii) in a previously sensitized person with strong immunity →solitary small papule (sites : dorsal hands , ankle , buttocks) → become hyperkeratotic = verrucous wart → never ulcerates → heal spontaneously
- HPE : pseudo epitheliomatous hyperplasia of epidermis and hyperkeratosis – superficial granulomatous inflammation in dermis – scanty AFB

**180. All of the following can cause SLE except :**

a. Hydralazine
b. Penicliin
c. Isoniazid
d. Sulphonamides

**Penicillin**

**181. Young female with moderate acne and irregular menstruation can be given ⊗?**

a. Isotretinoin oral
b. Acetretinoin oral
c. Minocycline oral
d. Cyproteron acetate oral

Cyproteron acetate oral

**Anesthesia**

**182. Adrenocortical suppression is caused by :**

a. Propfol
b. Etomidate
c. Ketamine
d. Halothane

**Etomidate**

**183. Patient of MS with abnormal LFT the anesthetic agent preferred is**

a. Halothane
b. Sevoflurane
c. Enflurane
d. Xenon

**Sevoflurane**

**Liver failure & Anesthetic agents**

| | Safe | Caution | C/I |
|---|---|---|---|
| **Premedication** | Lorazepam | Midazolam diazepam | |
| **Induction** | Propofol etomidate | | |

| | | | |
|---|---|---|---|
| **Maintainance** | **Des / Sevo/Iso flurane** NO | Enflurane | Halothane |
| **Muscle relaxants** | Atra/cisatra curium | Pan /Ve curonium Sch | |
| **Opioids** | Remifentanil | Fentanyl morphine pethidine | |
| **Analgesics** | PCM | NSAIDs lignocaine bupivacaine | |

**184. Post thoracotomy sever pain can be reduced by :**
a. Intercostals cryoanalgesia
b. Oral opioid
c. i.v. fentanyl
d. diclofenac suppository

**Intercostals cryoanalgesia**
•

**185. Concentration of K+ in RL :**
a. 1 meq/L
b. 2 meq/L
c. 4 meq/L
d. 6 meq/L

**4 meq/L**

| | **RL** | **NS** |
|---|---|---|
| **Mosm/L** | 273 (isotonic) | 308 (isotonic) |
| **Na+ (meq/L)** | 130 | 154 |
| **K+** | **4** | |
| **Cl-** | 109 | 154 |
| **Ca++** | 3 | |

**186. 40 year old male patient with RTA with severe maxillofacial injuries SPO2 80% , BP 100/70 , PR 120/min . immediate management is :**
a. i.v. fluids
b. orotracheal intbation
c. nasotracheal intubation
d. tracheostomy

**Orotracheal intubation**
- patient with facial injuries may have good airway immidately after blow → swelling of tongue,pharynx , face → obstruct airway soon
- this occurs specially if middle 3rd of face is involves (as in lefort III #)
- **inset an <u>oropharyngeal airway</u> even though patient is conscious and airway is not obstructed** – otherwise later on you have to do a risky emergency racheostomy

**187. a 70 kg athelete posted for emergency surgery. Due to nonavailability of vecuronium , Sch was given repeatedly in intermittent dose (total 650 mg). patient had undergone prolonged apnea with difficulty in moving limbs and respiratory fatigue. Most likely cause is :**
a. Deficiency of pseudocholineesterase
b. Phase 2 block
c. Muscular dystrophy
d. Fasciculations and paralysis of muscle

**Phase 2 block**
- Sch > 10 mg : causes phase 2 block
- Sch > 500 mg : exaggerated phase 2 block
- Rx : intubation and ventilation till recovery

**Radiology**

**188. Least risk of radiation exposure:**
a. IVP
b. MCU
c. Bilateral nephrostogram
d. CT spiral

**MCU**

**189. Best view for frontal sinus :**
a. Town's
b. Water's
c. Caldwell's
d. Schuller's

**Caldwell's**

| **View** | **Best sees** |
|---|---|
| **Town's (ear view )** | **Mandibular condyles middle ear – mastoid – cocjlear promontory – orbital floor** |
| **Water's** | **Maxillary sinus** |
| **Caldwell's** | **Frontal sinus** |
| **Schuller's** | **Mastoid** |

**190. A 25 year male with abdominal pain . clinical examination of chest and abdomen is normal. On CT retroperitoneal heterogenous mass seen on left renal hiulm . most likely diagnosis is :**

a. Lymphoma
b. Metastaic transitional Ca
c. Metastatic germ cell tumor
d. Metastatic melanoma

**Metastatic germ cell tumor**

- Retroperitoneal heterogenous mass = retroperitoneal necrotic LN
- Testicular malignancy : in 15-35 yr male – 1st spread to RPLN at renal hilum (more on left side long testicular vessels) – present with backache
- Lymphoma : same feature – but necrosis is rare before radiotherapy

**191. A person is posted for coronary angiogram. S.creatinine 2 mg/dl . all can be used to prevent contrast nephropathy except :**

a. Fenaldopam
b. Hemofiltration
c. N-acetyl cysteine
d. Half NS

**Half NS**

Contrast induced nephropathy

- Absolute increase in S.creatinine >0.5 mg/dl within 3 days of contrast administration is indicative of CIN
- Self limited : resolved in 1-3 week
- Permenant kidney damage is Uncommon
- Risk facrors for CIN
  - Old age
  - Dehydration
  - Multiple myeloma
  - Nehrotoxic drugs : NSAIDs
  - Prteinuria
- Pathophysiology : vaculolization of PCT cells & necrosis of medullary Ascending loop of henle
- Protection :
  - Use low osmolar contrasts : iodixanol
  - Normal saline (better than half NS)
  - Isotonic bicarbonate ± N-acetyl cysteine
  - Fenaldopam
  - Theophylline
  - CCBs
  - Hemofilatration (but prophylactic hemodialysis offer no protection)

**192. All are true about contrast CT of adrenal adenoma except : (repeat)**

a. Homogenous density with well defined margin
b. Low attenuation
c. Contrast is taken up early and wash out slowly
d. Calcification is rare

Contrast is taken up early and wash out slowly

**193. A 29 year female patient with cavernous sinus tumor and 6th nervepalsy . on T2 MRI hyper intense homognous enhancement is seen. Most probable diagnosis :**

a. Cavernous hemangioma
b. Meningioma
c. Astrocytoma
d. Schwanoma

**Meningioma ?**

**Psychiatry**

**194. Young male c/o voices commenting on his actions , voices abusing him and talking about him. His family members tells that he talks to himself and fearfulness since 2 days . he has fever since 2 days too. Diagnosis :**

a. Dementia
b. Acute psychosis
c. delirium
d. Delusional disorder

**Acute psychosis**

- **2 days – 2 weeks**
- Sudden onset
- Young patient (20-30 yrs)
- Associated personality disorders
- With or without symptomps of schizophrenia
- Delusions +/-

**195. A 30 yr lady develops acute attack of doom sensation , breathlessness , chocking , palpitation diagnosis:**

a. Panic disorder
b. Anxiety disorder
c. Conversion disorder
d. Acute psychosis

**Panic disorder**

**196. A girl is getting headache while studying , vision is normal , which of the following history is of least usefulness in diagnosis :**

a. Interest in studies
b. Family history of headache
c. Menstrual history
d. Self expectations

**Family history**

**Tension headache :**

- Risk factors for stress : interest in studies , self expectations should be asked
- Hormonal factors : menstrual history should be asked
- Alcohol/drug abuse
- Inadequate sleep
- Irregular diet
- No relation to family history

**197. True about late onset schizophrenia is;**

a. Onset after 45 years
b. Onset at 20-30 years
c. Bad prognosis
d. Olfactory hallucination

**Occurs after 45 years**

**Late onset schsizophrenia = paraphrenia (kreplin)**

- Onset > 45 years
- More common in women
- More prevalence of paranoid schizophrenia
- Hallucination absent/bizarre (taste/smell) : not a definitive feature
- Respond well to antipsychotics
- Good prognosis

**198. Anterograde amnesia is MC seen in :**

a. Post traumatic head injury
b. Stroke
c. Alzheimer
d. Spinal cord injury

**Post traumatic head injury**

| **Anterograde amnesia** | Retrograde amnesia |
|---|---|
| Amnesia for new events | Unable to recall past events |
| **Brain trauma** (hippocampus) > BZD induced amnesia | Diencephalic amnestic syndromes = korsakoff syndrome |

**199. A 70 year patient with 6 months history of progressive dementia with intermittent jerky movement of entire body for 2 days . EEG shows biphasic wave pattern . likely diagnosis is :**

a. CJD
b. Lewy body dementia
c. Alzhiemere
d. Herpes simplex encephalitis

**CJD**

- **Myclonus (intermittent jerky movement) & biphasic EEG pattern are characteristic of CJD**
- Age : 55-70
- Rapidly progressive dementia
- Mean duration : less than 6 months

Lewy body demention : r/o as n history of altered sensorium/psychotic symptomps

Alzhiemer's : r./o as it is slowly preogressive and insidious onset with triphasic EEG

Herpes simplex encephalitis : r/o as it shows amnesia with seizures & temporal localization of EEG

Molecular Diagnosis of Genetic Diseases : The molecular diagnosis of inherited diseases at the nucleic acid level has distinct advantages over other surrogate techniques:

- Molecular assays are **remarkably sensitive**.
- DNA-based tests **are not dependent on a gene product** that may be **produced only in certain specialized cells (e.g., brain) or expression of a gene that may occur late in life.** Because the defective gene responsible for inherited genetic disorders is present in germ line samples, every postzygotic cell carries the mutation.

## INDICATIONS FOR ANALYSIS OF GERM LINE GENETIC ALTERATIONS

*Prenatal genetic analysis* should be offered to all patients who are at risk of having cytogenetically abnormal progeny. It can be performed on cells obtained by amniocentesis, on chorionic villus biopsy material, or on umbilical cord blood. Some important indications are as follows

- A mother of **advanced age (>35 years)** because of greater risk of trisomies
- A parent who is a **carrier** of a balanced reciprocal translocation, robertsonian translocation, or inversion (in these cases the gametes may be unbalanced, and hence the progeny would be at risk for chromosomal disorders)
- A parent with a **previous child** with a chromosomal abnormality
- A fetus with **ultrasound-detected** abnormalities
- A parent who is a **carrier of an X-linked genetic disorder** (to determine fetal sex)
- **Abnormal** levels of AFP, βHCG, and estriol performed as the **triple test.**

*Postnatal genetic analysis* is usually performed on **peripheral blood lymphocytes**. Indications are as follows:

- Multiple congenital anomalies
- Unexplained mental retardation and/or developmental

delay

- Suspected aneuploidy (e.g., features of Down syndrome)
- Suspected unbalanced autosome (e.g., Prader-Willi syndrome)
- Suspected sex chromosomal abnormality (e.g., Turner syndrome)
- Suspected fragile-X syndrome
- Infertility (to rule out sex chromosomal abnormality)
- Multiple spontaneous abortions (to rule out the parents as carriers of balanced translocation; both partners should be evaluated)

## INDICATIONS FOR ANALYSIS OF ACQUIRED GENETIC ALTERATIONS

### *Diagnosis and management of cancer*

- Detection of tumor-specific acquired mutations and cytogenetic alterations that are the hallmarks of specific tumors (e.g., *BCR-ABL1* in chronic myeloid leukemia or CML)
- Determination of clonality as an indicator of a neoplastic (i.e., nonreactive) condition
- The identification of specific genetic alterations that can direct therapeutic choices (e.g., *HER2/Neu* [official name *ERBB2*] in breast cancer or *EGFR* mutations in lung cancer)
- Determination of treatment efficacy (e.g., minimal residual disease detection of BCR-ABL1 by PCR in CML)
- Detection of Gleevec-resistant forms of chronic myeloid leukemia and gastrointestinal stromal tumors

### *Diagnosis and management of infectious disease*

- Detection of microorganism-specific genetic material for definitive diagnosis (e.g., HIV, mycobacteria, human papillomavirus, herpesvirus in central nervous system)
- The identification of specific genetic alterations in the genomes of microbes that are associated with drug resistance
- Determination of treatment efficacy (e.g., assessment of viral loads in HIV and hepatitis C virus infection)

## PCR → DETECTION OF DNA SEQUENCE ALTERATIONS

- PCR analysis : By using appropriate DNA polymerases and thermal cycling, the **target DNA is greatly amplified**, producing millions of copies of the DNA sequence between the two primer sites. The subsequent identification of an abnormal sequence can then be performed using an ever-increasing number of assays.

### Direct Detection of DNA Sequence Alterations by DNA Sequencing

- DNA can be sequenced to obtain a readout of the order of nucleotides, and by comparison with a normal (wild-type) sequence, **mutations can be identified**.
- The ready availability of **Sanger di-deoxynucleotide sequencing** and **automated capillary electrophoresis** allows thousands of base pairs of genomic DNA to be routinely sequenced in a matter of hours.
- The genes mutated in hundreds of mendelian disorders have been identified, and definitive diagnosis is possible by direct sequencing in most of them.
- Some disorders, most with recessive inheritance, are associated with a limited number of recurrent mutations, such as cystic fibrosis.
- Many others, especially those with dominant inheritance, can have mutations throughout the gene-coding region.
- Challenges to sole use of gene sequencing for the diagnosis of such diseases include the difficulty and high cost of analyzing large genes.
- For example, the gene associated with Duchenne muscular dystrophy possesses 79 exons, and the *FBN1* gene mutated in Marfan syndrome possesses 65 exons; the sequencing of these genes in their entirety can be prohibitively expensive with current methodologies.
- Among other difficulties, it is not uncommon to detect **sequence alterations of unknown significance**, which cannot be definitively determined to be pathogenic in the absence of any functional data.

One high-throughput technology uses **gene chips (microarrays)** to sequence genes or portions of genes.

- Short sequences of DNA (oligonucleotides) that are complementary to the wild-type sequence and to known mutations are “tiled” adjacent to each other on the gene chip, and the DNA sample to be tested is hybridized to the array
- . Before hybridization the sample is labeled with fluorescent dyes.
- The hybridization (and consequently, the fluorescent signal emitted) will be strongest at the oligonucleotide that is complementary to wild-type sequence if no mutations are present,
- while the presence of a mutation will cause hybridization to occur at the complementary mutant oligonucleotide.
- Computerized algorithms can then rapidly “decode” the DNA sequence for hundreds of thousands of base pairs of sequence from the fluorescent hybridization pattern on the chip, and identify potential mutations.

“next-generation” sequencing

- which involves PCR performed in an oil emulsion that allows over one million individual PCR reactions at once.

- While at present very costly, over one billion nucleotides (one third of the human genome!) can be sequenced per run.

**Detection of DNA Mutations by Indirect Methods**

There are a large number of molecular techniques that detect DNA mutations without direct sequencing. Their development is driven by lower costs and higher throughput.

- One simple approach takes advantage of the digestion of DNA with enzymes known as **restriction enzymes** that recognize, and then cut, DNA at specific sequences. If the specific mutation is known to affect a restriction site, then the amplified DNA can be digested. Because the mutation affects a restriction site, the mutant and normal alleles give rise to PCR products of different sizes. These would appear as different bands on agarose gel electrophoresis. Needless to say, this approach is considerably less comprehensive than direct sequencing but remains useful for molecular diagnosis when the causal mutation always occurs at an invariant nucleotide position.
- Another approach for **identifying mutations at a specific nucleotide position** (say, a codon 12 mutation in the *KRAS* oncogene that converts glycine [GGT] to aspartic acid [GAT]) would be to add fluorescently labeled nucleotides C and T to the PCR mixture, which are complementary to either the wild-type (G) or mutant (A) sequence, respectively. Since these two nucleotides are labeled with different fluorophores, the fluorescence emitted by the resulting PCR product can be of one or another color, depending on whether a "C" or a "T" becomes incorporated in the process of primer extension . The advantage of this "**allele-specific extension" strategy** is that it can detect the presence of mutant DNA even in heterogeneous mixtures of normal and abnormal cells (for example, in clinical specimens obtained from individuals with a suspected malignancy).
- A variety of **PCR-based** technologies that use **fluorophore indicators** can detect the presence or absence of mutations in **"real time"** (i.e., during the exponential phase of DNA amplification). This has significantly **reduced the time** required for mutation detection by removing the restriction digestion and electrophoresis steps used in conventional PCR assays.
- **Mutations that affect the length of DNA (e.g., deletions or expansions)** can also be detected **by PCR analysis**. As discussed earlier, several diseases, such as the fragile-X syndrome, are associated with trinucleotide repeats. Two primers that flank the region affected by trinucleotide repeats at the 5′ end of the *FMR1* gene are used to amplify the intervening sequences. Because there are large differences in the number of repeats, the size of the PCR products obtained from the DNA of normal individuals, or those with premutation, is quite different. These size differences are revealed by differential migration of the amplified DNA products on a gel. At this point the full mutation cannot be detected by PCR analysis, because the affected segment of DNA is too large for conventional PCR. In such cases, a **Southern blot** analysis of genomic DNA must be performed (see "Southern Blotting").

## POLYMORPHIC MARKERS AND MOLECULAR DIAGNOSIS

Detection of mutations by the methods outlined above is possible only if the gene responsible for a genetic disorder is known and its sequence has been identified. In some diseases that have a genetic basis such approaches are not possible, either because the causal gene has not been identified or because the disease is multifactorial and no single gene is involved. In such cases, surrogate markers in the genome, also known as marker loci, can be used to localize the chromosomal regions of interest, on the basis of their linkage to one or more putative disease-causing genes. *Linkage analysis* deals with assessing these marker loci in family members having the disease or trait of interest, with the assumption that marker loci very close to the disease allele are transmitted through pedigrees (linkage disequilibrium). With time it becomes possible to define a "disease haplotype" based on a panel of marker loci, all of which co-segregate with the putative disease allele. Eventually, linkage analysis facilitates localization and cloning of the disease allele. The marker loci used in linkage studies are naturally occurring variations in DNA sequences known as *polymorphisms*. Two types of genetic polymorphism are most useful for linkage analysis. They are SNPs (including small insertion-deletion polymorphisms) and repeat-length polymorphisms known as minisatellite and microsatellite repeats. Each of the two types is described next.

SNPs occur at a frequency of approximately one nucleotide in every stretch of approximately 1000 base pairs and are found throughout the genome (e.g., in exons and introns and in regulatory sequences). They serve both as a physical landmark within the genome and as a genetic marker whose transmission can be followed from parent to child. Because of their prevalence throughout the genome and relative stability, SNPs can be used in linkage analysis for identifying haplotypes associated with disease.

Human DNA contains short repetitive sequences of DNA giving rise to what are called *repeat-length polymorphisms*. These polymorphisms are often subdivided on the basis of their length into microsatellite repeats and minisatellite repeats. Microsatellites are usually less than 1 kilobase and are characterized by a repeat size of 2 to 6 base pairs. Minisatellite repeats, by comparison, are larger (1–3 kilobases), and the repeat motif is usually 15 to 70 base pairs. It is important to note that the number of repeats, both in microsatellites and minisatellites, is extremely variable within a given population, and hence these stretches of DNA can be used quite effectively to establish genetic identity for linkage analysis. Microsatellites and the smaller minisatellites can be readily

distinguished by utilizing PCR primers that flank the repeat region ( Fig. 5-33A ). Note that in the example given in Figure 5-33 , three different alleles generate PCR products of different lengths (hence the name "length polymorphism")

Linkage analysis can be been useful in the antenatal or presymptomatic diagnosis of disorders such as Huntington disease and autosomal dominant polycystic kidney disease, even though the disease-associated gene is known in each of these conditions. In general, when the disease-associated gene is known, detection of the causative mutation by direct sequencing is the method of choice. However, if the disease originates from several different mutations in a given gene (e.g., *fibrillin-1*; see earlier), and gene sequencing is either not practical or negative but there is very strong clinical suspicion, linkage analysis can be useful. Figure 5-33B illustrates how microsatellite polymorphisms can be used to track the inheritance of autosomal-dominant polycystic kidney disease. In this case allele C, which produces a larger PCR product than allele A or B, carries the disease-related gene. Hence all individuals who carry the C allele are affected.

Assays to detect genetic polymorphisms are also important in many other areas of medicine, including in the determination of relatedness and identity in transplantation, cancer genetics, paternity testing, and forensic medicine. Since microsatellite markers are scattered throughout the human genome and have such a high level of polymorphism, they are ideal for differentiating two individuals and to follow transmission of the marker from parent to child. Panels of microsatellite marker PCR assays have been extensively validated and are now routinely used for determining paternity and for criminal investigations. Since PCR can be performed even with highly degraded biologic samples, DNA technology is critical in forensic identifications. The same assays have been applied to the detection and quantification of transplant chimerism in allogeneic bone marrow transplants.

Polymorphisms and Genome-Wide Analyses

As described earlier, linkage analysis utilizing DNA of affected families has been used to detect the presence of genes with large effects and high penetrance, the kind that give rise to Mendelian diseases. Similar analyses of complex (multifactorial) disorders, however, have been unsuccessful since conventional linkage studies lack the statistical power to detect variants with small effects and low penetrance, which are typical of the genes that contribute to complex disorders.

These limitations appear to have been overcome through genome-wide association studies (GWAS), a powerful method of identifying genetic variants that are associated with an increased risk of developing a particular disease.[78] Such variants may themselves be causative, or may be in *linkage disequilibrium* with other genetic variants that are responsible for the increased risk. In GWAS large cohorts of patients with and without a disease (rather than families) are examined across the entire genome for genetic variants or polymorphisms that are over-represented in patients with the disease. This identifies regions of the genome that contain a variant gene or genes that confer disease susceptibility. The causal variant within the region is then provisionally identified using a "candidate gene" approach, in which genes are selected based on how tightly they are associated with the disease and whether their biologic function seems likely to be involved in the disease under study. For example, a variant in a gene whose product regulates vascular smooth muscle tone (e.g., angiotensinogen) is a strong candidate to influence the risk of hypertension. As might be imagined, however, some linked genes would not have been expected to be associated with particular diseases based on prior knowledge; such surprises are one of the benefits of the unbiased, systematic nature of GWAS.

GWAS have been enabled by two major technological breakthroughs. First is the completion of the so-called "HapMap" project, which has provided more complete linkage disequilibrium patterns in three major ethno-racial groups, based on genome-wide single nucleotide polymorphism (SNP) mapping. The entire human genome can now be divided into blocks known as "haplotypes," which contain varying numbers of contiguous SNPs on the same chromosome that are in linkage disequilibrium and hence inherited together as a cluster. As a result, rather than querying every single SNP in the human genome, it is possible to glean comparable information about shared DNA by simply looking for shared haplotypes, using single or a small number of SNPs that "tag" or identify a specific haplotype. Second, it is now possible to simultaneously genotype hundreds of thousands to a million SNPs at one time, in a cost-effective way, using high-density SNP-chip technology. Figure 5-34 demonstrates how information from the publicly available "HapMap" is utilized to manufacture SNP chips that can query genome-wide haplotypes in an unbiased manner. Thereafter, DNA from a cohort of individuals with a defined trait (say, hypertension) is analyzed using SNP chips for haplotypes that are overrepresented compared to individuals without the trait (i.e., in controls). This is followed by the "candidate gene" approach described above to further localize the causal gene (and in some instances, the functional polymorphism within that gene), associated with the trait

In addition to shedding light on some of the most frequent human ailments such as diabetes, hypertension, coronary artery disease, schizophrenia and other mental disorders, and asthma, GWAS have also led to the identification of genetic loci that modulate common quantitative traits in humans, such as height, body mass, hair and eye color, and bone density. An updated catalog of published GWAS is maintained by the National Human Genome Research Institute

(www.genome.gov ), with the list currently at >200 studies and growing. The power of GWAS is underscored by the fact that within a very short time, nearly a dozen genes that confer risk for type 2 diabetes have been identified, of which one in particular, *TCF7L2*, has emerged as a strong candidate gene (see Chapter 24 for a detailed discussion).

With the incrementally lowered costs for genotyping individual patients for SNPs that might render them "at-risk"

for a variety of multifactorial disease over their lifetime, there is emerging concern in the biomedical community that such information would be utilized for discrimination in the workplace or by healthcare agencies. In the United States, a law was passed in 2008 that explicitly prohibits discrimination based on an individual's genetic makeup.

**MOLECULAR ANALYSIS OF GENOMIC ALTERATIONS** : A significant number of genetic lesions involve large deletions, duplications, or more complex rearrangements that are **not easily assayed using PCR methods or sequence analysis**. Such "genomic" alterations can be studied using a variety of hybridization-based techniques.

**Southern Blotting**

- Changes in the structure of specific loci can be detected by Southern blotting,
- which involves hybridization of radiolabeled sequence-specific probes to genomic DNA that has been first digested with a restriction enzyme and separated by gel electrophoresis.
- The probe usually detects one germ line band in normal individuals.
- Importantly, a normal DNA sample is required to compare the pattern of the DNA in question.
- With the advent of FISH and microarray technology, Southern blotting is **rarely used** but **remains useful in**
  - the detection of large-**trinucleotide-expansion diseases** including the fragile-X syndrome and
  - in detection of **clonal immunoglobulin gene rearrangements** in the diagnosis of lymphoma. : replaced by PCR-based methods

**Fluorescence in Situ Hybridization**

- FISH uses DNA probes that recognize sequences specific to particular chromosomal regions.
- As part of the Human Genome Project, large libraries of bacterial artificial chromosomes that span the entire human genome were created.
- The human DNA insert in these clones is on the order of 100,000–200,000 base pairs, which defines the limit of resolution of FISH for identifying chromosomal changes.
- These DNA clones are labeled with fluorescent dyes and applied to metaphase spreads or interphase nuclei.
- The probe hybridizes to its homologous genomic sequence and thus labels a specific chromosomal region that can be visualized under a fluorescent microscope.
- The **ability of FISH to circumvent the need for dividing cells** is invaluable when a **rapid diagnosis** is warranted (e.g., when deciding to treat a patient with acute myeloid leukemia with retinoic acid, which is only effective in a particular subtype with a chromosomal translocation involving the retinoic acid receptor gene).
- FISH can be performed on prenatal samples (e.g., cells obtained by amniocentesis, chorionic villus biopsy, or umbilical cord blood), peripheral blood lymphocytes, touch preparations from cancer biopsies, and even archival tissue sections.
- FISH has been used
  - for detection of numeric abnormalities of chromosomes (aneuploidy)
  - for the demonstration of subtle microdeletions or complex translocations not detectable by routine karyotyping;
  - for analysis of gene amplification (e.g., *HER2/NEU* in breast cancer or *N-MYC* amplification in neuroblastomas); and
  - for mapping newly isolated genes of interest to their chromosomal loci.
- **Chromosome painting** is an **extension of FISH**, whereby probes are prepared for entire chromosomes.
- The number of chromosomes that can be *detected simultaneously* by chromosome painting is limited by the availability of fluorescent dyes that emit different wavelengths of visible light.
- This limitation has been overcome by the introduction of **spectral karyotyping** (also called **multicolor FISH**).
- By using a combination of five fluorochromes and appropriate computer-generated signals, the entire human genome can be visualized . So powerful is spectral karyotyping that it might well be called "spectacular karyotyping."

**Micro array = Array-Based Comparative Genomic Hybridization (Array CGH)**

- FISH requires prior knowledge of the one or few specific chromosomal regions suspected of being altered in the test sample.
- However, genomic abnormalities can also be detected **without prior knowledge of what these aberrations** may be, using a global strategy such as array CGH.
- In array CGH the test DNA and a reference (normal) DNA are labeled with two different fluorescent dyes (most commonly Cy5 and Cy3, which fluoresce red and green, respectively) .
- The differentially labeled samples are then hybridized to a glass slide spotted with DNA probes that span the human genome at regularly spaced intervals, and usually cover all 22 autosomes and the X chromosome.
- If the contributions of both samples are equal for a given chromosomal region (i.e., the test sample is diploid), then all spots on the array will fluoresce yellow (the result of an equal admixture of green and red dyes).
- In contrast, if the test sample shows an excess of DNA at any given chromosomal region (such as resulting from an amplification), there will be a corresponding excess of signal from the dye with which this sample was labeled.
- The reverse will be true in the event of a deletion, with an excess of the signal used for labeling the reference sample.
- Amplifications and deletions in the test sample can now be significantly better localized, often down to a few thousand base pairs.

- Newer arrays provide even higher resolution with more than 100,000 probes per array, and are at present being used to uncover copy number abnormalities in a variety of diseases, from cancer to autism.
- Array CGH is regularly performed in cases of mental retardation–developmental delay of unknown etiology or in children with dysmorphic features with negative karyotypes
- CNVs are a recently discovered source of genetic polymorphism, which was uncovered using array CGH technology. While intriguing in terms of understanding the marked differences between individual genomes, they can be problematic in the clinical interpretation of array CGH data.
- There are usually many CNVs observed when comparing any two genomes encompassing millions of bases of DNA.
- Deciding whether a specific change is a benign polymorphism or a critical disease-causing duplication or deletion can be difficult. Databases of CNVs now exist that are very helpful guides in deciding on the relevance of questionable CNVs. Another limitation of existing array CGH platforms is that they cannot detect balanced translocations, since there is a rearrangement but no genetic material is gained or lost. Nonetheless, the vastly superior sensitivity of molecular approaches should make assays such as array CGH first-line genomic diagnostic tests that have the potential of replacing traditional karyotyping.

## EPIGENETIC ALTERATIONS

*Epigenetics is defined as the study of heritable chemical modification of DNA or chromatin that does not alter the DNA sequence itself.* Examples of such modification include the methylation of DNA, and the methylation and acetylation of histones. Our understanding of these types of molecular alterations is rapidly growing, and it is clear that epigenetic modifications are critical for normal human development—including the regulation of tissue-specific gene expression, X chromosome inactivation, and imprinting, as well as for understanding of the cellular perturbations in the aging process and cancer.[80,][81]

Gene expression frequently correlates with the level of methylation of DNA, usually of cytosines specifically in the CG dinucleotide-rich promoter regions known as CpG islands. As discussed earlier in the section on genomic imprinting, increased methylation of these loci is associated with decreased gene expression and is accompanied by concomitant specific patterns of histone methylation and acetylation. An ever-increasing number of disease states warrant analysis of promoter methylation—for example, in the diagnosis of fragile-X syndrome, in which hypermethylation results in *FMR1* silencing. Methylation analysis is also essential in the diagnosis of Prader-Willi and Angelman syndromes.

Since traditional Sanger sequencing alone cannot detect DNA methylation, other techniques have been developed to uncover these chemical modifications. One common approach is to treat genomic DNA with sodium bisulfite, a chemical that converts unmethylated cytosines to uracil, while methylated cytosines are protected from modification. An assay termed methylation-specific PCR uses two PCR primer sets to analyze single DNA loci: one to detect a DNA sequence with unmethylated cytosines (which are converted to uracils after bisulfite treatment) and the other to detect DNA sequences with methylated cytosines (which remain cytosines after bisulfite treatment).[82] Additional techniques are evolving that provide a genome-wide snapshot of epigenetically altered DNA. These techniques are based on the ability to detect histone modifications such as methylation and acetylation (which, like DNA methylation, are important regulators of gene expression) by using antibodies against specifically modified histones. Such antibodies can be used to pull down bound DNA sequences, a method termed chromatin immunoprecipitation (ChIP). These pulled-down sequences can be amplified and analyzed by hybridizing to microarrays ("ChIP on Chip") or sequencing ("ChIP-Seq") to map epigenetically modified genes throughout the genome.[83,][84]

## RNA ANALYSIS

Changes in DNA lead to alterations in mRNA expression; hence in principle it should be possible to use mRNA expression analysis in the diagnosis of genetic diseases. From a practical standpoint, however, DNA-based diagnosis is much preferred, since DNA is much more stable. Nonetheless, RNA analysis is critical in several areas of molecular diagnostics. The most important application is the detection and quantification of RNA viruses such as HIV and hepatitis C virus. Furthermore, mRNA expression profiling (described in Chapters 7 and 23 is rapidly becoming an important tool for molecular stratification of tumors. In some instances cancer cells bearing particular chromosomal translocations are detected with greater sensitivity by analyzing mRNA (e.g., *BCR-ABL* fusion in CML). The principal reason for this is that most translocations occur in scattered locations within particular introns, which can be very large, beyond the capacity of conventional PCR amplification. Since introns are removed by splicing during the formation of mRNA, PCR analysis is possible if RNA is first converted to cDNA by reverse transcriptase. PCR performed on cDNA is the method of choice for detection of minimal residual disease in patients with chronic myeloid leukemia ( Chapter 13 ).

In closing, it should be pointed out that the progress in unraveling the genetic basis of human disease promises to be breathtaking in the coming years. An entirely new field of personalized and genomic medicine is waiting to be developed.