ENDOCRINOLOGY

Hormone

Definition –

- It is a substance that is produced by a endocrine gland in one part of the body, passes into the bloodstream and is carried to other organs or tissues,
- Where it acts to –
    - Modify their structures or function & Elicit cellular responses.
    - Regulate physiologic processes through feedback mechanisms.

Term Hormone was coined by Starling

Classification:

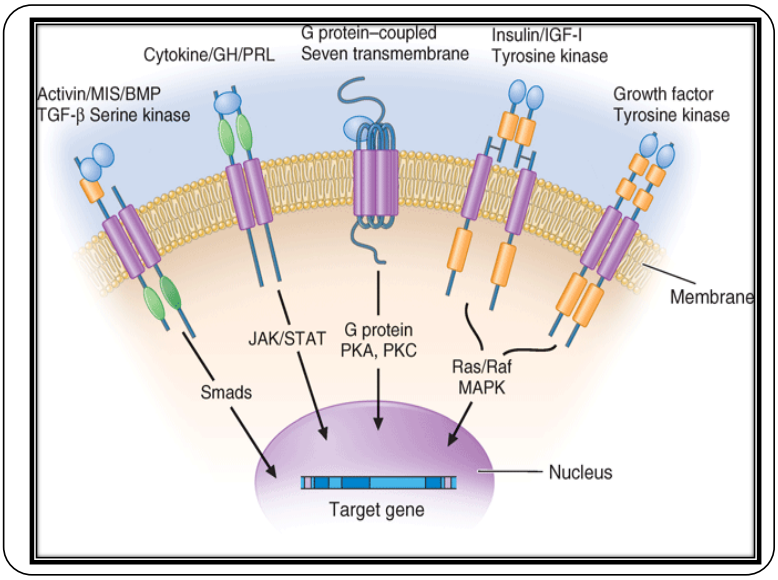
Hormones can be divided into **five major classes** based on their underlying ***structure:***

1. Steroid hormones such as cortisol and estrogen
2. Vitamin derivatives such as retinoids and vitamin D.
3. Amino acid derivatives such as dopamine, catecholamines and thyroid hormone.
4. Small neuropeptides such as GnRH, TRH etc.
5. Large proteins such as insulin, LH, PTH etc.

Classification acc. to Receptors

Membrane Receptor Families

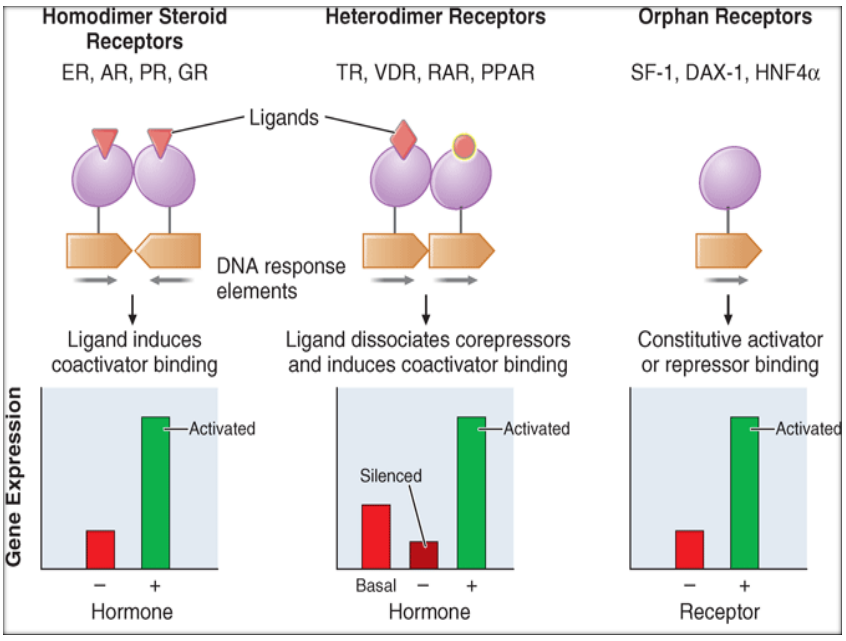
1. **G Protein–Coupled Seven-Transmembrane (GPCR)** -EX:-Beta-Adrenergic, Alfa-Adrenergic, LH, FSH, TSH, ACTH MSH, GHRH, CRH,Somatostatin ,TRH, GnRH, Glucagon PTH, PTHrP.
2. **Receptor Tyrosine Kinase** -EX:- Insulin, IGF-I,EGF, NGF,etc.
3. **Cytokine Receptor–Linked Kinase** aka JAK (Janus Associated Kinase)-EX:- GH, PRL.
4. **Serine Kinase** -EX:- Activin, TGF-beta, MIS.



Nuclear Receptors

EX:-

- **Steroid hormones** such as Cortisol,Aldosterone,Androgen,Progesterone,Estrogen,Testosterone &Vitamin derivatives such as retinoids and vitamin D
- And Thyroid hormone.



Synthesis of Hormone

- **Peptide hormones-**
    - Genes code for messenger RNA, which is then translated into protein precursors.
    - These proteins undergo posttranslational cleavage and/or processing to form the active hormone
- **Steroid hormones-**
    - The precursor-cholesterol (for most steroid hormones) or 7-dehydrocholesterol (for vitamin D metabolites) - undergoes a series. of enzymatic transformations to form the final products.

Cross-Reactions b/t hormone receptors: Specificity Spill over phenomena

- Hormone binding - highly specific for a single type of receptor, specially for nuclear type.
- Exceptions:-

1. TSH with the LH or the FSH
2. Insulin and insulin-like growth factor I (IGF-I) and IGF-II .
3. Cross-talk is seen with PTH and parathyroid hormone–related peptide
4. Mineralocorticoid receptor also binds glucocorticoids with high affinity in renal tubular cells .
5. The glycoprotein hormones family, consisting of-thyroid stimulating hormone, follicle stimulating hormone, luteinizing hormone, and human chorionic gonadotropin - share the alpha sub-unit in common; the beta sub-unit are distinct and confer specific biological actions. There is some cross reaction between various hormones of glycoprotein family, thus very high levels of HCG during pregnancy or in states like HCG secreting neoplasms stimulate the TSH receptor and increase thyroid hormone levels.
6. This is an example of specifity spill over phenomena.
7. Other examples of the same being Insulin & IGF family of peptides, Gh & prolactin.

Of the various types of hormones enumerated above, steroids, thyroid

hormones, vitamin D, and retinoids are lipid-soluble and interact with intracellular nuclear receptors. Usually hormone binding is highly specific for a single type of nuclear receptor. One exception to this rule is the presence of highly related glucocorticoid and mineralocorticoid receptors. Thus glucocorticoids bind to mineralocorticoid receptors with great affinity (although, reverse is not true), and an enzyme called 11beta-hydroxysteroid dehydrogenase type 2 (present in renal tubular cells) achieves mineralocorticoid specificity, by inactivating cortisol and allowing selective response to aldosterone. However, when very high glucocorticoid concentrations occur, as in Cushing's syndrome, the glucocorticoid degradation pathway becomes saturated, allowing excessive cortisol levels to exert mineralocorticoid effects (sodium retention, potassium wasting) by acting on mineralocorticoid receptors.. The phenomenon is particularly pronounced in ectopic ACTH syndromes.

RELEASE

Release of hormones into the blood stream can involve

- **conversion of insoluble to soluble derivatives** (proteolysis of thyroglobulin to thyroid hormones),
- **exocytosis of storage granules** (insulin, glucagon, prolactin, growth hormone), or
- **passive diffusion** of newly synthesized molecules such as steroid hormones down activity gradients into plasma.

Transport

Many hormones circulate in association with serum-binding proteins.

Examples

- T4 and T_3 binding to thyroxine- binding globulin , albumin, and thyroxine-binding prealbumin
- Cortisol binding to cortisol-binding globulin (CBG);etc.

These interactions -

- Provide a hormonal reservoir, prevent otherwise rapid degradation of unbound hormones, and
- Modulate the unbound, or "free," hormone concentrations.

Only unbound hormone is available to interact with receptors & thus elicit biologic response.

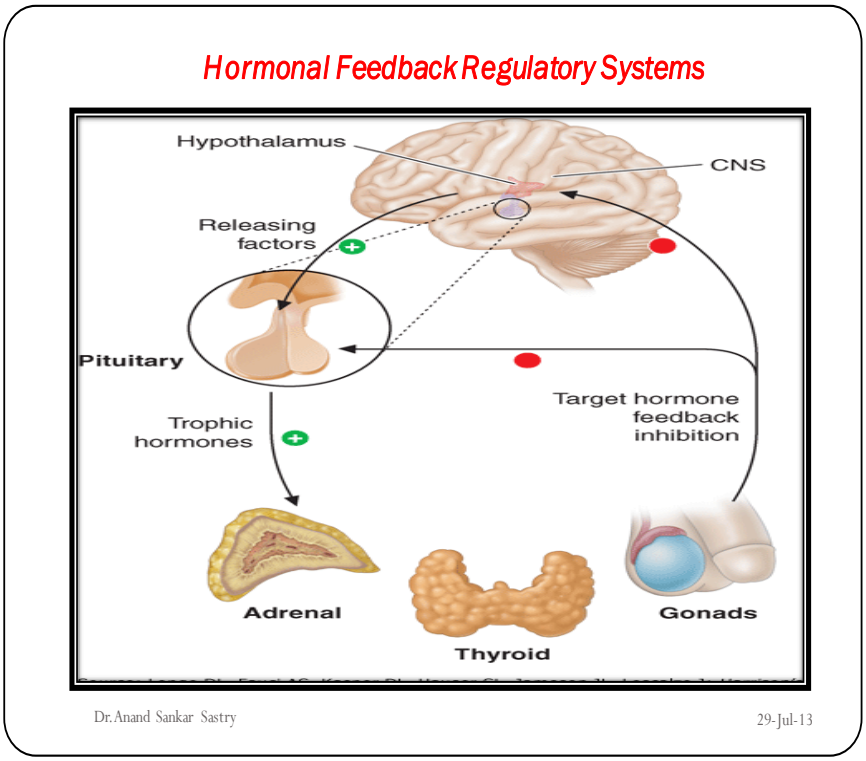
Functions of Hormones

Growth:-Ex-GH,Thyroid hormone,Cortisol,Sex steroids.

Maintenance of Homeostasis:-

- Thyroid hormone—controls about 25% of basal metabolism in most tissues
- Cortisol—exerts a permissive action for many hormones in addition to its own direct effect
- PTH—regulates calcium and phosphorus levels
- Vasopressin—regulates serum osmolality by controlling renal free-water clearance
- Mineralocorticoids—control vascular volume and serum electrolyte (Na^+, K^+)
- Insulin—maintains euglycemia in the fed and fasted states.

Reproduction:-Ex:-Testosterone,Estrogen&Progesterone,FSH,LH,GnRH



Hormonal Rhythms-

- The feedback regulatory systems are superimposed on hormonal rhythms that are used for adaptation to the environment.

- **Seasonal changes, the daily occurrence of the light-dark cycle, sleep, meals, and stress** are examples of the many environmental events that affect hormonal rhythms

Pathologic Mechanisms of Endocrine Disease

Endocrine diseases can be divided into three major types of conditions:

- (1) hormone excess,
- (2) hormone deficiency
- (3) hormone resistance

HYPERFUNCTION	
Neoplastic	
Benign	Pituitary adenomas, hyperparathyroidism, autonomous thyroid or adrenal nodules, pheochromocytoma
Malignant	Adrenal cancer, medullary thyroid cancer, carcinoid
Ectopic	Ectopic ACTH, SIADH secretion
MEN	MEN 1, MEN 2
Autoimmune	Graves' disease
Iatrogenic	Cushing's syndrome, hypoglycemia
Infectious/inflammatory	Subacute thyroiditis
Activating receptor mutations	LH, TSH, Ca2+ and PTH receptors, Gs

Hypofunction	
Autoimmune	Hashimoto's thyroiditis, Type 1 diabetes mellitus, Addison's disease, polyglandular failure
Iatrogenic	Radiation-induced hypopituitarism, hypothyroidism, surgical
Infectious/inflammatory	Adrenal insufficiency, hypothalamic sarcoidosis
Hormone mutations	GH, LH , FSH, vasopressin
Enzyme defects	21-Hydroxylase deficiency
Developmental defects	Kallmann syndrome, Turner syndrome, transcription factors
Nutritional/vitamin deficiency	Vitamin D deficiency, iodine deficiency
Hemorrhage/infarction	Sheehan's syndrome, adrenal insufficiency
Hormone resistance	
By Receptor mutations	
Membrane	GH, Vasopressin, LH, FSH, ACTH, GnRH, GHRH, PTH, leptin, Ca2+
Nuclear	AR, TR, VDR, ER, GR, PPAR
Post receptor	Type 2 diabetes mellitus, Leptin resistance

Hormone Measurements

- Immunoassays: Ex-IRMA,ICMA:-
- Using antibody to capture the antigen (hormone) onto an immobilized surface and a second antibody, coupled to a-
    - Chemiluminescent [immunochemiluminescent assay (ICMA)]
    - Radioactive immunoradiometric assay (IRMA)] signal, to detect the antigen.
- Detect plasma hormone concentrations in the picomolar to nanomolar range, and they can readily distinguish structurally related proteins, such as PTH from PTHrP
- **Sample-**
- Most hormone measurements -based on plasma or serum sample
- Urinary collections over 24 h- provide an integrated assessment of the production of a hormone or metabolite that vary during a day.
- A 24-h urine free cortisol measurement -reflects unbound cortisol
- Other commonly used urine determinations include-
    - 17-hydroxycorticosteroids, 17-ketosteroids,
    - Vanillylmandelic acid, metanephrine,
    - Catecholamines, 5-hydroxyindoleacetic acid, and calcium
- Much information can be gained from **basal hormone testing**, when **different components of an endocrine axis** are assessed simultaneously.
- All are based on principles of feedback regulation

DYNAMIC TESTING--

- ***Suppression tests –***
    - Used in the setting of suspected endocrine hyperfunction
    - Example - dexamethasone suppression test used to evaluate Cushing's syndrome
- ***Stimulation tests***

- Used to assess endocrine hypofunction.
- Ex:-The ACTH stimulation, CRH and GHRH stimulation,Insulin-induced hypoglycemia.

DIABETES MELLITUS

- **Most common** endocrine disease.
- It is a metabolic syndrome characterized by-
  - **Hyperglycemia** due to absolute or relative deficiency of insulin.
  - This leads to alteration of the metabolism of carbohydrate, protein and fat,
  - Manifests with various metabolic abnormalities and by long-term complications involving the *nerves, eyes, kidneys, and blood vessels*

CLASSIFICATION

- New classification - Based on **pathogenic process**
- Earlier criteria – based onage of onset or type of therapy.
- New classification **differs from** the previous classifications on two aspects:
  - The terms IDDM & NIDDM are obsolete.

Age is not a criterion for the classification of subtypes.

Etiologic Classification of Diabetes Mellitus

- I- In type 1 diabetes,
  - **Beta cell destruction**, leading to absolute insulin deficiency.
- II- In type 2 diabetes-
  - **Insulin resistance** (main defect) followed by **impaired insulin secretion, and ↑glucose production**
- III. Other specific types of diabetes
- IV- Gestational DM

DIAGNOSIS

Revised criteria (**ADA 2011**) for diagnosing DM :

- Fasting plasma glucose (FPG) ≥ 126 mg% or
- Symptoms of diabetes plus random plasma glucose ≥ 200 mg % or
- Two hour after 75 g of oral load of glucose, plasma glucose ≥ 200 mg%

HbA1C level of > 6.5%.

Criteria for the Diagnosis of Diabetes*

		INCREASED RISK*			
Test	Normoglycemia	Impaired Fasting Glucose	Impaired Glucose Tolerance	High Risk	Diabetes†
PG, fasting (mg/dL)	<100	100-125			≥126
PG, 2-hour (mg/dL)	<140		140-199		≥200
Hemoglobin A_{1c} (%)				5.7-6.4	≥6.5
PG, casual (mg/dL)					>200 mg/dL plus symptoms of diabetes

*Risk for diabetes is continuous, extending below the lower limit and becoming disproportionately greater at the higher end of the ranges shown.
†In the absence of unequivocal hyperglycemia, a diagnostic result should be confirmed by repeat testing.
Adapted from American Diabetes Association. Standards of medical care in diabetes—2010. *Diabetes Care.* 2010;29:s11-s61.

- **Fasting is defined**,
    - As no caloric intake for at least 8 h.
- In the absence of unequivocal hyperglycemia and acute metabolic decompensation, these criteria should be confirmed- by **repeat testingon a different day.**
- Revised criteria also allow for the diagnosis of DM **to be withdrawn** in situations where the FPG no longer exceeds these criteria.
- **A1C or the FPG -** the most reliable and convenient tests for identifying DM in asymptomatic individuals**.**

Pre-diabetes

- Impaired Glucose Tolerance" (IGT) - If the 2-h value in GTT is between *140 and 200 mg/dL, (or A1C of 5.7–6.4%)*
- Impaired fasting glucose (IFG) is *analogous to impaired glucose tolerance.*
- Glucose tolerance can also be classified based on the FPG:
    - FBG < 100 mg% (Normal)
    - FBG b/w 100 -125 mg% (IFG)
    - FBG ≥ 126 mg % (DM)

- IFG or IGT- recently designated as-
    - Pre-diabetes/ "increased risk of diabetes" (ADA),
    - "Intermediate hyperglycemia" (WHO)
- *Substantial risk for* developing –
    - Type 2 DM (25-40% risk over the next 5 years)
    - Cardiovascular disease in the future.

Screening-

Recommended because

(1) Most are -Asymptomatic and unaware,

(2) Type 2 DM may be present for up to a decade before diagnosis,

(3) Type 2 DM people may have complications at the time of their diagnosis

(4) Treatment of type 2 DM may have a favorably outcome

The ADA recommends screening-

- All individuals >45 years every 3 years
- Earlier age if they are overweight [body mass index (BMI) >25 kg/m^2] & have one additional risk factor for diabetes.

In Asia (prevalence increasing) & its different from USA & Europe-

- Onset at a lower BMI
- Younger age,
- Greater visceral adiposity,

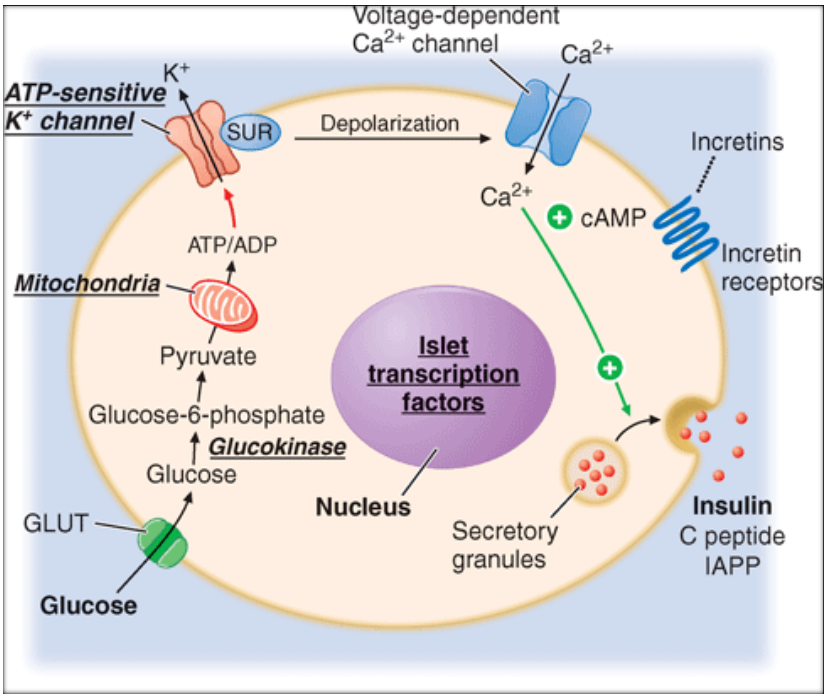
Reduced insulin secretory capacity.

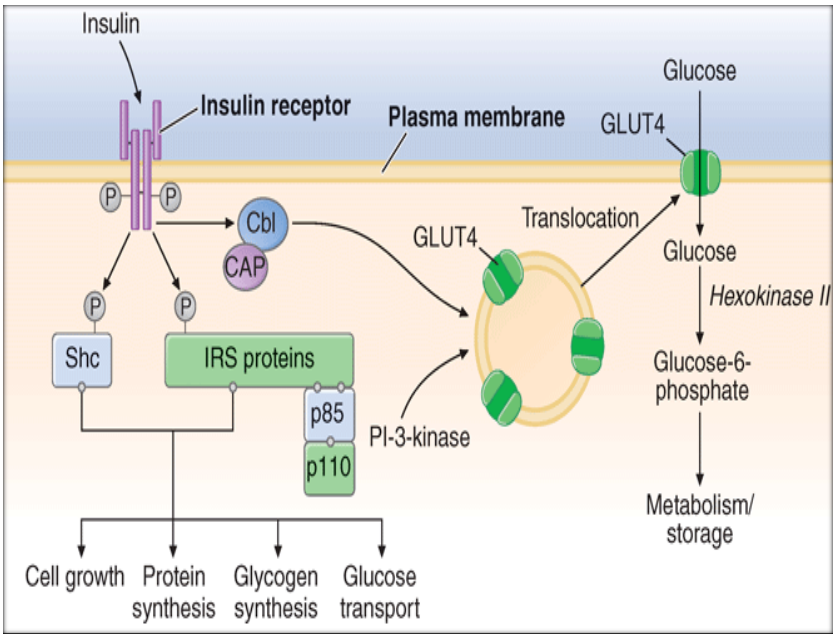
Risk Factors for Type 2 Diabetes Mellitus

- Family history of DM
- Obesity (BMI 25 kg/m^2)& Physical inactivity,
- Race/ethnicity
- Previously identified with IFG, IGT, or an A1C of 5.7–6.4%

- HDL cholesterol level <35 mg/dL
- Triglyceride level >250 mg/dL ,
- H/o GDM or delivery of baby >4 kg
- H/o Hypertension (140/90 mmHg)
- H/o POCD or acanthosis nigricans
- H/o cardiovascular disease

Insulin Biosynthesis, Secretion, and Action-





- **Glucose homeostasis** reflects a balance between-
    - Hepatic glucose production
    - Peripheral glucose uptake and utilization.
- **Regulator of Glucose homeostasis -**
    - Insulin (most important)
    - Neural input, metabolic signals, and other hormones (e.g., glucagon)
- **In Fasting state:** Low insulin levels increase glucose by promoting-
    - Hepatic gluconeogenesis
    - Glycogenolysis
    - Reduce glucose uptake in insulin-sensitive tissues (skeletal muscle and fat),
    - Mobilization of stored amino acids and free fatty acids (lipolysis).
- **Glucagon,** secreted by pancreatic alpha cells when-
    - Blood glucose or insulin levels are low, stimulates glycogenolysis and gluconeogenesis by the liver and renal medulla.
- **Postprandially**-

- Increase glucose load elicits a **rise in insulin and fall in glucagon**
- Insulin, an anabolic hormone, promotes the storage of carbohydrate and fat and protein
- Postprandial glucose - utilized by skeletal muscle (by insulin-stimulated glucose uptake)

- **Incretins –**
  - Released from neuroendocrine cells of GIT following food ingestion
  - Amplify insulin secretion and suppress glucagon secretion.
- Glucagon-like peptide 1 (GLP-1)- most potent incretin,
- Incretin analogues, are used to enhance endogenous insulin secretion.
- Dipeptidyl peptidase 4 (DPP-4)-rapidly proteolyse GLP-1, so DPP-4 inhibitors are also used to enhance endogenous insulin secretion.

PATHOGENESIS OF TYPE 1 DIABETES

Genetic Considerations-Multiple genes involved.

- Identical twins – affected 40 to 60%.
- HLA region on chromosome 6- Major gene for type 1 DM.
- Polymorphisms in the HLA – accounts for 40–50% of the genetic risk
  - HLA DR3 and/or DR4 haplotype
  - Most strongly associated- Haplotypes DQA1*0301, DQB1*0302 DQB1*0201
- Although the risk of developing type 1 DM is increased tenfold in relatives of individuals with the disease, the risk is relatively low:
  - 3–4% if the parent has type 1 diabetes
  - 5–15% in a sibling
- Hence, most individuals with type 1 DM do not have a first-degree relative with this disorder

INSULITIS

- Insulitis-
    - Islet cell autoantibodies (ICA)
    - Activated lymphocytes in the islets,
    - Release of cytokines.
- Beta cells - particularly susceptible to cytokines [(TNF-), interferon & IL-1)]
- ICAs- produced against–
    - Insulin,
    - Glutamic acid decarboxylase (GAD), ICA-512/IA-2
- Immunologic Markers- Assays for autoantibodies to GAD-65
- ICAs-Present in the majority of individuals (>85%) diagnosed with type 1 DM.

Environmental Factors

- Viruses (Coxsackie, Rubella, Enteroviruses most prominently),
- Bovine milk proteins
- Nitrosourea compounds.

Associated Autoimmune Diseases

	AUTOANTIBODY		
Disease	Type	Percentage	Disease Prevalence (%)
Addison's disease[91]	21-Hydroxylase	1.5	0.5
Celiac disease[90]	Transglutaminase	12	6
Pernicious anemia[92]	Parietal cell	21	2.6
Thyroiditis or Graves' disease	Peroxidase or thyroglobulin	25	4

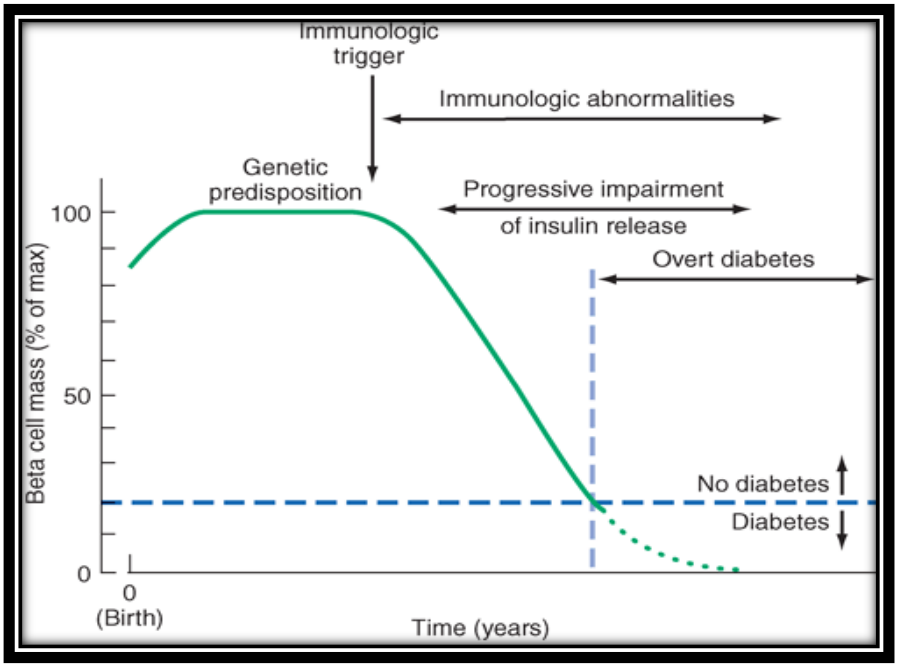
Latent autoimmune diabetes in adults

- **Some Type 2 DM people –**
    - May have *evidence of autoimmune activity* against pancreatic beta cells,

- May have a slowly evolving variant of type 1 DM called latent autoimmune diabetes in adults or LADA.

Temporal model for development of type 1 diabetes.

1.Individuals with a genetic predisposition are exposed to an immunologic trigger that initiates an autoimmune process, resulting in a gradual decline in beta cell mass.
2.The downward slope of the beta cell mass varies among individuals and may not be continuous.
3.This progressive impairment in insulin release results in diabetes when 80% of beta cell destroyed.
4. A "honeymoon" phase may be seen in the first 1 or 2 years after the onset of diabetes and is associated with reduced insulin requirements.

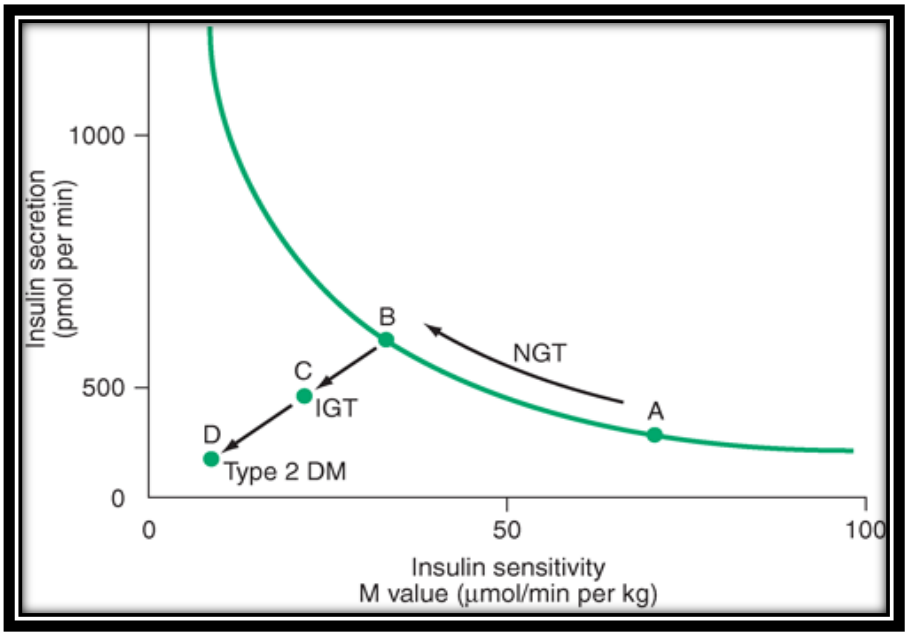


TYPE 2 DM(PATHOGENESIS)

- Type 2 DM is characterized by –
  - Impaired insulin secretion,
  - Insulin resistance,
  - Excessive hepatic glucose production
  - Abnormal fat metabolism.
- Obesity, particularly visceral or central

- Early stages -glucose tolerance remains near-normal (due to beta cells compensate by increasing insulin output)- hyperinsulinemia.
- Later stage-
    - Insulin resistance and compensatory hyperinsulinemia progress,
    - Pancreatic islets are unable to sustain the hyperinsulinemic state.
- IGT, characterized by elevations in postprandial glucose, then develops.
- Overt diabetes with fasting hyperglycemia - due to further decline in insulin secretion and an increase in hepatic glucose production
- Ultimately, beta cell failure ensues.

Insulin secretion and insulin sensitivity are related,
With more insulin resistant (by moving from point A to point B), insulin secretion increases.
A failure to compensate by increasing the insulin secretion results initially in impaired glucose tolerance (IGT; point C) and ultimately in type 2 DM (point D).



Genetic Considerations

- Strong genetic component.
- Identical twins - affected 70 to 90%.

- If both parents have type 2 DM, the risk approaches 40%.
- Polygenic and multifactorial,

Environmental factors

- Obesity, nutrition, and physical activity

Insulin resistance-

- Insulin resistance- the decreased ability of insulin to act effectively on target tissues (especially muscle, liver, and fat)
- Insulin dose-response curves exhibit a rightward shift, indicating reduced sensitivity, and a reduced maximal response, indicating an overall decrease in maximum glucose utilization.
- Insulin resistance impairs glucose utilization by insulin-sensitive tissues and increases hepatic glucose output; both effects contribute to the hyperglycemia.
- Increased hepatic glucose output predominantly accounts for increased FPG levels, whereas decreased peripheral glucose usage results in postprandial hyperglycemia.

Cause of insulin resistance-

- “Postreceptor" defects in insulin-regulated phosphorylation /dephosphorylation.
    - E.g- PI-3-kinase signaling defect might reduce translocation of GLUT4
- **Obesity (central or visceral)- causes insulin resistance**
    - Adipocytes secrete a number of biologic products (FFA, leptin, TNF-α, resistin, and adiponectin).
    - Free fatty acids impair glucose utilization in skeletal muscle, promote glucose production by the liver, and impair beta cell function.
    - Adiponectin, an insulin-sensitizing peptide, is reduced in obesity, and this may contribute to hepatic insulin resistance.

Insulin Resistance Syndromes

- Syndrome X Components-
    - Insulin resistance
    - hypertension
    - dyslipidemia (decreased HDL and elevated triglycerides),
    - central or visceral obesity,
    - type 2 diabetes or IGT/IFG,
    - accelerated cardiovascular disease.

Two distinct syndromes

(1) Type A-

- Affects young women
- Severe hyperinsulinemia, obesity, and features of hyperandrogenism;
- undefined defect in the insulin-signaling pathway;

(2) Type B-

- Affects middle-aged women
- Severe hyperinsulinemia, features of hyperandrogenism, autoimmune disorders.
- Autoantibodies directed at the insulin receptor.
- Insulin resistance is seen in a significant subset of women with PCOS.

Impaired Insulin Secretion-

- In type 2 DM, insulin secretion initially increases in response to insulin resistance to maintain normal glucose tolerance.
- Eventually, the insulin secretory defect progresses to a state of inadequate insulin secretion.
- A second genetic defect—superimposed on insulin resistance—leads to beta cell failure
- Beta cell mass is decreased by approximately 50% in long-standing type 2 diabetes.

- Islet amyloid polypeptide or amylin is co-secreted by the beta cell and forms the amyloid fibrillar deposit found in the islets of individuals with long-standing type 2 DM.
- High levels of glucose (“glucose toxicity”) or increased tissue levels of long-chain fatty acids ("lipotoxicity") could be playing role in worsening of islet function.

Increased Hepatic Glucose and Lipid Production-

- Liver reflects the failure of hyperinsulinemia to suppress gluconeogenesis, which results in fasting hyperglycemia and decreased glycogen storage by the liver in the postprandial state.
- As a result of insulin resistance in adipose tissue, lipolysis and free fatty acid flux from adipocytes are increased, leading to increased lipid [very low density lipoprotein (VLDL) and triglyceride] synthesis in hepatocytes.
- This lipid storage or steatosis in the liver may lead to nonalcoholic fatty liver disease and abnormal liver function tests.
- This is also responsible for the dyslipidemia found in type 2 DM [elevated triglycerides, reduced high-density lipoprotein (HDL), and increased small dense low-density lipoprotein (LDL) particles].

Prevention

- Intensive changes in lifestyle –
- Diet and exercise for 30 min/d five times/week)
- Maintain a normal BMI and engage in regular physical activity.
- Metformin – to IFG and IGT people who are at very high risk for progression to diabetes.
- Monitored annually - Individuals with IFG, IGT, or an A1C of 5.7–6.4%

3. Other specific types of diabetes

A. Genetic defects of beta cell characterized by mutations in:

1. Hepatocyte nuclear transcription factor (HNF) 4α (MODY 1)
2. Glucokinase (MODY 2)

3. HNF-1α (MODY 3)-MC.

4. Insulin promoter factor-1 (IPF-1; MODY 4)

5. HNF-1β (MODY 5)

6. NeuroD1 (MODY 6)

7. Mitochondrial DNA

8. Subunits of ATP-sensitive potassium channel

9. Proinsulin or insulin

B. Genetic defects in insulin action-Type A&B insulin resistance

C. Diseases of the exocrine pancreas-pancreatitis, cystic fibrosis, hemochromatosis,etc.

D. Endocrinopathies-acromegaly, Cushing's syndrome, pheochromocytoma, hyperthyroidism,etc.

E. Drug- or chemical-induced —glucocorticoids, thiazides, hydantoins,etc.

F. Infections—congenital rubella, cytomegalovirus, coxsackievirus

H.Other genetic syndromes— Wolfram's syndrome, Down's syndrome, Klinefelter's syndrome, Turner's syndrome, etc.

Maturity-onset diabetes of the young (MODY)

- **Subset of DM, characterized by-**
    - Autosomal dominant inheritance,
    - Early onset of hyperglycemia (usually <25 years),impairment in insulin secretion ,
    - Response to Sulfonylureas in some cases.
    - In Non-Obese persons-Resistant to Ketosis.
- **Six different variants of MODY , Type—3 is most common.**

Transient or permanent neonatal diabetes (onset <6 m age)

- **Mutations in-**

- ATP-sensitive potassium channel subunits
- Insulin gene (interfere with proinsulin folding and processing)

- **Respond to sulfonylureas**
- **Associated with a spectrum of neurologic dysfunction**

Diagnostic criteria for MODY

- Non insulin dependent-shown by –
  - Absence of insulin treatment 5 years after diagnosis or
  - Significant C-peptide in a patient on insulin treatment.
- Rarely obese
- Early diagnosis of diabetes-before 25 years one and two (ideally) family members
- Autosomal dominent inheritance i.e vertical transmission in two (at least) or three (ideally) generations
- Diabetes results from beta cell dysfunction-
  - Insulin levels are often in the normal range,
  - Though inappropriately low for degree of hyperglycemia

	Type 1	**Type 2**	**Mody**
Age of onset	**Predominantly young, (<20 yr)**	**Predominantly middle to old age(>30 years)**	**Predominantly young(<25 years)**
Genetic	**30-70% concordance in twins,polygenic inheritance**	**50-90% concordance in twins,polygenic inheritance**	**100% concordance in twins,Autosomal Dominent Inheritance**
Family History	**Not significant, only 6% children of**	• **Significant,** • **40% children**	• **Significant,** • **Vertical transmissio**

	affected children develop disease.	**develop disease if both parents affected** • **Vertical transmission - not essenial for diagnosis**	**n- through atleast two(ideally three) - essenial for diagnosis**
HLA Association	**Yes(DR3,DR4)**	**No**	**No**
Pathogenesis	**Autoantibodies to beta cells, Insulitis**	**No autoantibody, No insulitis, Insulin resistance Common.**	**Beta cell dysfunction to glucose for insulin secretion, No insulitis, No Insulin Resistance**
Presence of other autoimmune disorders such as autoimmune thyroid disease, adrenal insufficiency, pernicious anemia, celiac disease, and vitiligo.	**Usually present**	**Absent**	**Absent**
Presence of associated conditions such as insulin resistance, hypertension, cardiovascular disease, dyslipidemia(Mainl	**Absent**	**Usually present**	**Absent**

y Hypertriglyceride mia), or PCOS			
Presence of Autoimmune markers like GAD, ICA-512/IA-2	**Present**	**Absent**	**Absent**
Presence of complications at time of diagnosis	**Uncommon**	**common**	**Uncommon**
Ketoacidosis	**common**	**Rare**	**Rare**
Non-Ketotic Hyperosmolar coma	**Rare**	**common**	**Rare**
Insulin necessary in treatment	**always**	**Sometimes**	**Sometimes**
Obesity	**Uncommon**	**common**	**Uncommon**
Insulin level	• **Markedly decreased blood insulin,** • **Absolute insulin deficiency**	• **Increased Insulin(Early),** • **Normal to moderately decreased insulin(late)**	**Insulin levels are often in the normal range, though inappropriately low for degree of hyperglycemia**
Classic symptom of polyuria, polydipsia,etc	**common**	**Rare**	**Rare**

IV. Gestational diabetes mellitus (GDM) –

- Glucose intolerance developing during pregancy.
- Insulin resistance- related to the metabolic changes of late pregnancy
- Increased insulin requirements may lead to IGT or diabetes.
    - Most women- revert to normal glucose tolerance postpartum
    - But have risk (35–60%) of developing DM in the next 10–20 yr.
- The International Diabetes and Pregnancy Study Groups-

Recommends Diabetes diagnosed at the initial prenatal visit to use "overt" diabetes rather than gestational diabetes.

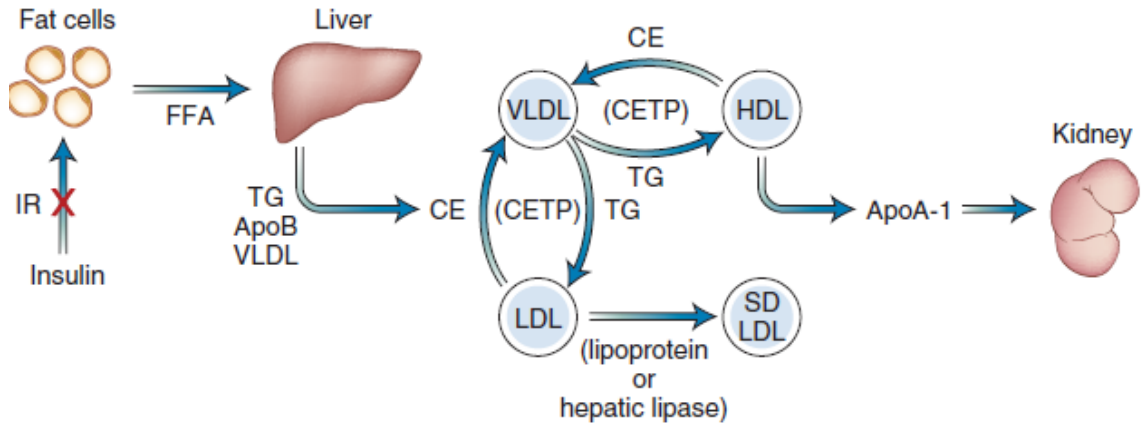
LONG-TERM TREATMENT-

Goals of therapy for type 1 or type 2 DM are to:

- Eliminate *symptoms* related to hyperglycemia,
- Reduce or eliminate the long-term microvascular & macrovascular *complications* of DM
- Allow the patient to achieve as normal a *life-style*

SYNDROME X AND LADA:

- A characteristic feature of type 2 DM is that it is often associated with other medical disorders including obesity, hypertension and hyperlipidemias. This cluster of conditions is together known as SYNDROME X or REAVEN'S SYNDROME or METABOLIC SYNDROME or INSULIN RESISTANCE SYNDROME. It is strongly associated with atherosclerosis and is often manifested by macrovascular diseases of cerebral, coronary and peripheral vascular system with associated increased mortality. Some people with apparent type 2 DM have evidence of autoimmune activity against pancreatic beta cells, and may have a slowly evolving variant of type 1 DM called latent autoimmune diabetes in adults or LADA.



- **Insulin resistance (IR) to the characteristic dyslipidemia of type 2 diabetes mellitus.**
- IR at the adipocyte results in increased free fatty acid (FFA) release. Increased FFA flux stimulates secretion of very-low-density lipoprotein (VLDL), causing hypertriglyceridemia (TG).
- VLDL stimulates a reciprocal exchange of TG to cholesteryl ester (CE) from both high-density lipoprotein (HDL) and low-density lipoprotein (LDL), catalyzed by CE transfer protein (CETP). TG-enriched HDL dissociates from apolipoprotein (Apo) A-1, leaving less HDL for reverse cholesterol transport. TG-enriched LDL serves as a substrate for lipases that convert it to atherogenic small, dense LDL particles (SD LDL).

TREATMENT GOALS FOR ADULTS WITH DIABETES

INDEX	**GOAL**
Glycemic control	
A1C (primary goal)	**<7%**
Fasting capillary plasma glucose	**70-130 mg%**
Peak postprandial capillary plasma	**<180 mg%**

glucose	
Blood pressure	
Patients with reduced GFR and macroalbuminuria	**<125/75**
Others	**<130/80**
Lipids (in decreasing order of priority)	
LDL	**<100mg% (if CAD present, it should be < 70 mg%)**
HDL	**>40mg% in men and > 50 mg% in women**
TGA	**<150mg%**

- **MEDEM (monitoring, education, diet, exercise, medications)**
- **MONITORING-**
    - SMBG-Short-term glycemic control
    - HbA1C reflects average glycemic control over the previous 2–3 months.
- **SMBG Vs HbA1C-**
    - *Recent intercurrent illnesses* may impact the SMBG measurements but not the HbA1c.
    - *Postprandial and nocturnal hyperglycemia* – detected only by HbA1c.

Self-Monitoring of Blood Glucose

- *Type 1 DM -*
- *Need frequent monitoring four to eight times per day*
- *To estimate and select mealtime boluses of short-acting insulin and to modify long-acting insulin doses.*

- *Type 2 DM - require less frequent monitoring.*
- *Continuous glucose monitoring systems (CGMS)*
- *Devices for continuous blood glucose monitoring,*
- *Measure the glucose in interstitial fluid (by injecting subcutaneous sensor) that is in equilibrium with the blood glucose*

Glycated hemoglobin or HbA1c-

- Principle- When plasma glucose is consistently elevated, there is an increase in nonenzymatic glycation of hemoglobin; this alteration reflects the glycemic history over the previous 2 to 3 months, since RBC life span is of 120 days
- Glycemic level in preceding month contributes about 50% to the A1C
- Frequency of Monitoring-
  - During their initial evaluation.
  - Every six months in patients achieving their glycemic goals
  - Every three months in patients whose glycemic control is inadequate, when treatment is changed, or in most patients with type 1 DM.
- HbA1c of 6% is 135 mg/dL. A 1% rise in the HbA1c translates into a 35 mg/dL increase in the mean glucose.

Laboratory methods :

- Done by -Electrophoresis, chromatography, immunoassays
- There is significant interassay variations
- *Falsely decreased*Hb A1C - hemoglobinopathies, hemolytic anemias, and pregnancy.
- *Falsely elevated* Hb A1C -uremia, alcohol abuse, or iron deficiency.

Fructosamine Assay (*Measuring Glycated Albumin*)-

- Alternative measure & reflects the glycemic status over the 1 to 2 prior weeks.
- Fructosamine is a better choice when A1C can’t be readily measured :

- Evaluation of changes in diabetic treatment
- In Pregnancy - glucose and insulin needs of mother and fetus changes rapidly during gestation.
- Condition where RBC age changes-hemolytic anemia, sickle cell or blood loss

- **DISADVANTAGES-**
  - Falsely low in conditions of decreased protein levels such as nephrotic syndrome or hepatic disease.
  - Lack of standardization and concern with reproducibility
  - Not recommended for routine use or replacement for A1C

Urine ketones

- Urine glucose - does not provide an accurate assessment of glycemic control,
- Urine ketones *are a sensitive indicators of early diabetic ketoacidosis and*should be measured in individuals with type 1 DM when:
- The plasma glucose is consistently > 300 mg/dL,
- During a concurrent illness, or
- With symptoms such as nausea, vomiting, or abdominal pain.

Blood measurement of β-hydroxybutyrate is preferred*over urine testing with nitroprusside-based assays that measure only acetoacetate and acetone* .

EDUCATION OF THE PATIENT-

- *Diet,*
- *Self-monitoring of blood glucose;*
- urine ketone monitoring (type 1 DM);
- insulin administration;
- diabetes management during illnesses;
- prevention and management of hypoglycemia

- foot and skin care;
- diabetes management before, during, and after exercise; and
- risk factor–modifying activities.

DIET-

Medical nutrition therapy (MNT) is a term used to describe the optimal coordination of caloric intake with other aspects of diabetes therapy (insulin, exercise, weight loss).

ADA has issued recommendations for three types of MNT.

- *Primary prevention measures* of MNT are directed at preventing or delaying the onset of type 2 DM in high-risk individuals (obese or with pre-diabetes) by promoting weight reduction.
- *Secondary prevention measures* of MNT are directed at preventing or delaying diabetes related complications in diabetic individuals by improving glycemic control.
- *Tertiary prevention measures* of MNT are directed at managing diabetes-related complications. For example in diabetic nephropathy, protein intake should be limited to 0.8 g/kg of body weight per day.

Nutritional Recommendations for Adults with Diabetes-

Weight loss diet (in prediabetes and type 2 DM)
Hypocaloric diet that is low-fat or low-carbohydrate
Fat in diet
Minimal *trans* fat consumption
Carbohydrate in diet
Monitor carbohydrate intake in regards to calories
Sucrose-containing foods may be consumed with adjustments in insulin dose
Amount of carbohydrate determined by estimating grams of carbohydrate in diet

for (type 1 DM)
Glycemic index reflects how consumption of a particular food affects the blood glucose
Protein in diet: as part of an optimal diet
Other components
Nonnutrient sweeteners
Routine supplements of vitamins, antioxidants, or trace elements not advised

Recommended diabetic diet should aim at achieving a BMI of 22.

Protein

- In general, protein should constitute 10-35% of the total calorie intake.
- Acceptable range is 1.0 to 1.5 g/kg per day, limited to 0.8 g/kg per day for diabetic Nephropathy.

Fat

- They should constitute 20-35%of total calorie intake.
- Monounsaturated fats are associated with an improved plasma lipid profile with reduction in total and LDL cholesterol.
- Trans-fat consumption should be minimal
- Dietary cholesterol should be <300 mg/day and individuals with LDL cholesterol more than 100 mg% should limit dietary cholesterol to <200 mg/day.

Carbohydrates

- A suitable diet for diabetics should have 45-65% of the daily caloric intake derived from carbohydrate, of which significant amount should be in the form of non-starch polysaccharide, as dietary fiber.
- *Mono- and disaccharides (fructose, sucrose and glucose) should be restricted*

- However, as per latest ADA recommendations, sucrose containing foods may be consumed with adjustment in insulin dose.
- Non-nutritive sweeteners *saccharin, aspartame, sucramate and acesulphame K* are the most widely used.
- Fiber (30 g/d) and sodium (≤ 3 g/d) levels as recommended.
- Should be careful while taking alcohol, not only because it accounts for extra calories, but also may potentiate the hypoglycemic action of sulfonylureas and insulin.
- In addition, alcohol predisposes towards the development of lactic acidosis in patients taking metformin.

Type 1 DM

- The goal of MNT in the individual with type 1 DM is to coordinate and match the caloric intake, with the appropriate amount of insulin.

Type 2 DM

- MNT for type 2 DM should emphasize modest caloric reduction, increased physical activity, and reduction of hyperlipidemia and hypertension.
- The majority of these individuals are obese, and weight loss is still strongly encouraged and should remain an important goal. .

EXERCISE

- Individuals with type II-
    - ADA recommends 150 min/week (distributed over at least 3 days) of aerobic physical activity.
- Individuals with type 1 DM-
    - Promote exercise-related hyper- or hypoglycemia
    - Exercise should delay exercise if blood glucose is > 250 mg/dL, < 100 mg/dL, or if ketones are present.
- Untreated proliferative retinopathy is a relative contraindication to vigorous exercise, since this may lead to vitreous hemorrhage or retinal detachment.

MEDICATION-

TYPE 1 DIABETES MELLITUS

- Administration of basal, exogenous insulin is essential
- Postprandial insulin replacement

Intensive Management

Tries to achieve euglycemia or near-normal glycemia using all available resources.

The benefits of intensive diabetes management and improved glycemic control include:

- A *reduction in the microvascular complications of DM* and a possible delay or reduction in the macrovascular complications of DM.
- In newly diagnosed patients with type 1 DM it *may prolong the period of C-peptide production*, which may result in better glycemic control and a reduced risk of serious hypoglycemia.
- In pregnancy, it *reduces fetal malformation and morbidity*.
- Lastly, it is indicated in patients who have had *kidney transplantation for diabetic nephropathy.*

Properties of Insulin Preparations

Time of Action			
Preparation	**Onset, h**	**Peak, h**	**Effective Duration, h**
Short-acting			
Aspart	**<0.25**	**0.5-1.5**	**3-4**
Glulisine	**<0.25**	**0.5-1.5**	**3-4**
Lispro	**<0.25**	**0.5-1.5**	**3-4**
Regular	**0.5–1.0**	**2-3**	**4-6**

Long acting Insulin

Preparation	Onset,h	Peak,h	Effective duration ,h
Detemir	**1-4**	**--**	**Upto 24**
Glargine	**1-4**	**--**	**Upto 24**
NPH	**1-4**	**6-10**	**10-16**
Insulin combinations			
75/25–75% protamine lispro, 25% lispro	**< 0.25**	**1.5 h**	**Upto 10-16**
70/30–70% protamine aspart, 30% aspart	**< 0.25**	**1.5 h**	**Upto 10-16**
50/50–50% protamine lispro, 50% lispro	**< 0.25**	**1.5 h**	**Upto 10-16**
70/30–70% NPH, 30% regular	**0.5-1**	**dual**	**10-16**

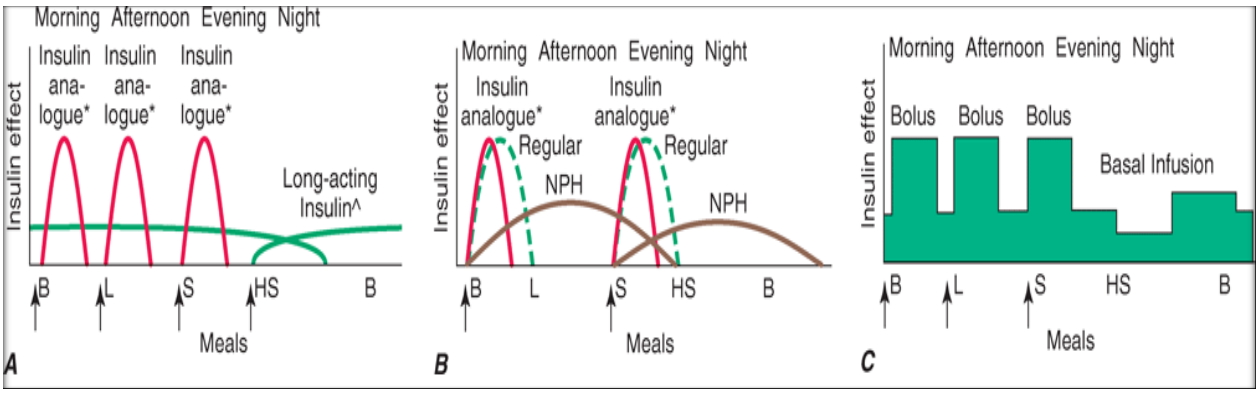
Insulin Regimens

Individuals with type 1 DM require 0.5–1 U/kg per day of insulin divided into multiple doses, with 50% of the insulin given as basal insulin.

1.Multiple-component insulin regimens refer to the combination of basal insulin and bolus insulin (preprandial short-acting insulin).

- The timing and dose of short-acting, preprandial insulin are altered to accommodate the SMBG results, anticipated food intake, and physical activity.
- To determine the meal component of the preprandial insulin dose, the patient uses an insulin-to- carbohydrate ratio (a common ratio for type 1 DM is 1–1.5 units/10 g of carbohydrate).

- To this insulin dose is added the supplemental or correcting insulin based on the preprandial blood glucose [1 unit of insulin for every 2.7 mmol/L (50 mg/dL) over the preprandial glucose target;].



2.One commonly used regimen consists of twice-daily injections of NPH mixed with a short-acting insulin before the morning and evening meals .

- Such regimens usually prescribe two-thirds of the total daily insulin dose in the morning (with about two-thirds given as long-acting insulin and one-third as short-acting) and
- one-third before the evening meal (with approximately one-half given as long-acting insulin and one-half as short-acting).
- The drawback to such a regimen is that it enforces a rigid schedule on the patient, in terms of daily activity and the content and timing of meals.

3.Continuous SC insulin infusion (CSII)

- Very effective insulin regimen for the patient with type 1 diabetes .
- To the basal insulin infusion, a preprandial insulin ("bolus") is delivered by the insulin infusion device based on instructions from the patient, who uses an individualized algorithm incorporating the preprandial plasma glucose and anticipated carbohydrate intake .
- These sophisticated insulin infusion devices can accurately deliver small doses of insulin (microliters per hour) and have several advantages:

(1) multiple basal infusion rates can be programmed to accommodate nocturnal versus daytime basal insulin requirement,

(2) basal infusion rates can be altered during periods of exercise,

(3) programmed algorithms consider prior insulin administration and blood glucose values in calculating the insulin dose.

Other agents that improve glucose control-

1.An analogue of amylin (pramlintide) -reduce postprandial glycemic excursions in type 1 and type 2 diabetic patients taking insulin.

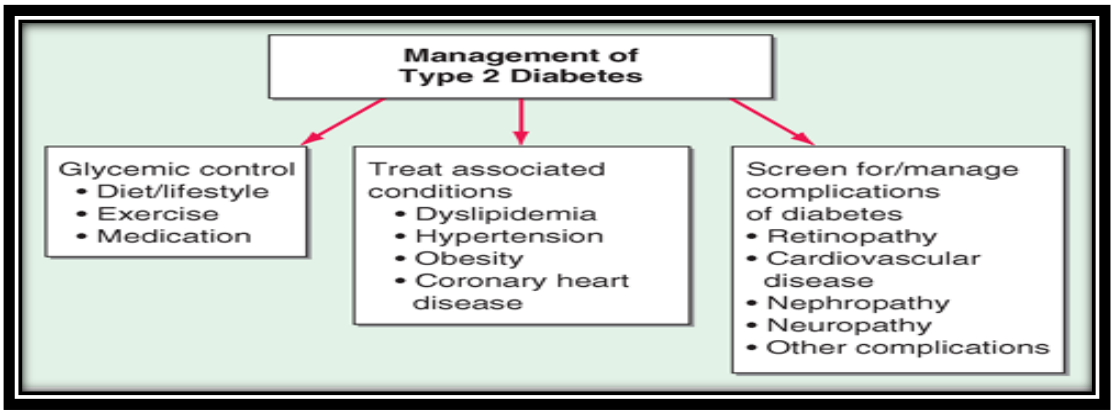
- Pramlintide is approved for insulin-treated patients with type 1 and type 2 DM.
- The major side effects are nausea and vomiting.

2. Alpha glucosidase inhibitors may be used in patients with type 1 DM.

<u>Early morning hyperglycemia-</u>

- Somogyi effect: here early morning hyperglycemia is secondary to nocturnal hypoglycemia, which in turn causes surge of counterregulatory hormones.
- These hormones produce high blood glucose levels by seven am.
- This can be diagnosed by 3 am sample of blood glucose, which shows *hypoglycemia*.
- Decreasing the evening dose of intermediate acting insulin improves morning hyperglycemia.

Management of Type 2 Diabetes Mellitus-



Agents Used for Treatment of Type 1 and Type 2 Diabetes

	Mechanism of Action	e.g	AIC reduction (%)	Agent-Specific Advantages	Agent-Specific Disadvantages	Contraindications
Oral						
Biguanides	**Hepatic glucose production**	**metformin**	**1-2**	**Weight neutral, Do not cause hypoglycemia, inexpensive**	**Diarrhea, nausea, lactic acidosis**	**Serum creatinine >1.5 mg/dL (men) >1.4 mg/dL (women), CHF, radiographic contrast studies, seriously ill patients, acidosis**
-Glucosidase inhibitors[b]	**GI glucose absorption**	**Acarbose, Miglitol**	**0.5-0.8**	**Reduce postprandial glycemia**	**GI flatulence, liver function tests**	**Renal/liver disease**
Dipeptidyl peptidase IV inhibitors	**Prolong endogenous GLP-1 action**	**Saxagliptin, Sitagliptin, Vildagliptin**	**0.5-0.8**	**Do not cause hypoglycemia**		**Reduce dose with renal disease**
Insulin	**Insulin**	**Glipi**	**1-2**	**Inexpensi**	**Hypoglycemi**	**Renal/li**

secretagoguesSulfonylureas	**secretion**	**zide, Glicazide, Glibenclamide, Glimepiride**		**ve**	**a, weight gain**	**ver disease**
Insulin secretagogues: Non-sulfonylurea	**Insulin secretion**	**Repaglinide,Nateglinide**	**1-2**	**Short onset of action, lower postprandial glucose**	**Hypoglycemia**	**Renal/liver disease**
Thiazolidinediones[b]	**↓Insulin resistance,glucose utilization**	**Rosiglitazone, Pioglitazone**	**0.5–1.4**	**Lower insulin requirements**	**Peripheral edema, CHF, weight gain, fractures, macular edema; rosiglitazone may increase cardiovascular risk**	**CHF, liver disease**
Insulin	**Glucose utilization, Hepatic glucose production, and other anabolic actions**		**Not limited**	**Known safety profile**	**Injection, weight gain, hypoglycemia**	

GLP-1 receptor agonists[b]	**↑Insulin, ↓glucagon, slow gastric emptying, satiety**	**Exenatide, liraglutide**	**0.5 - 1.0**	**Weight loss, do not cause hypoglycemia**	**Injection, nausea, risk of hypoglycemia with insulin secretagogues, pancreatitis, renal failure**	**Renal disease, agents that also slow GI motility;**
Amylin agonists	**Slow gastric emptying, glucagon**	**Pramlintide**	**0.25 - 0.5**	**Reduce postprandial glycemia; weight loss**	**Injection, nausea, risk of hypoglycemia with insulin**	**Agents that also slow GI motility**

Insulin Therapy in Type 2 DM-

Insulin should be considered as the initial therapy in type 2 DM in

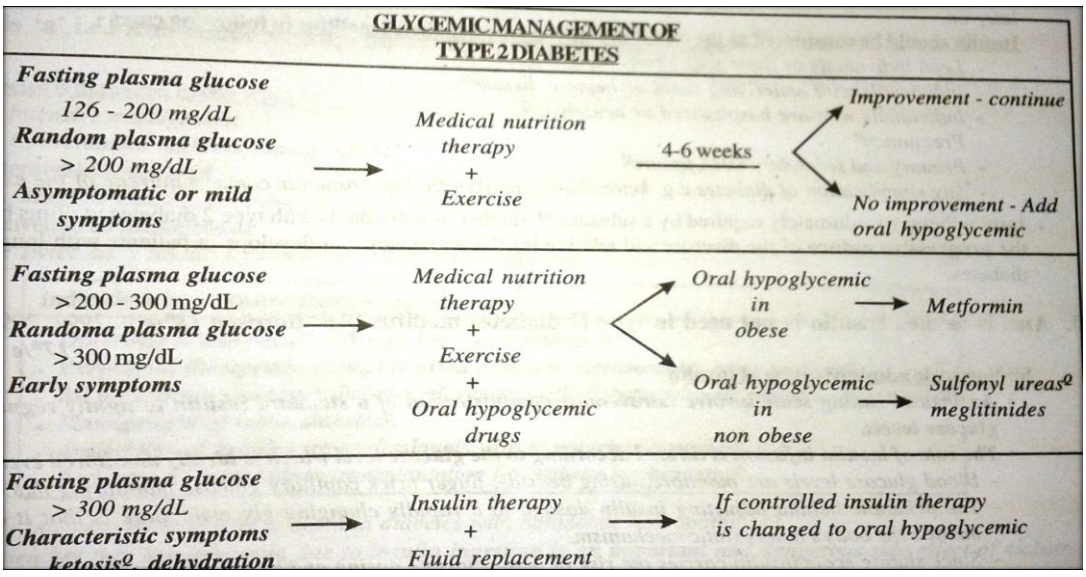
- Lean individuals or those with severe weight loss,
- Underlying renal or hepatic disease that precludes oral glucose-lowering agents, or
- Hospitalized or acutely ill.

Insulin therapy-

- Required by few individuals with type 2 DM

- Because of the progressive nature of the disorder and the relative insulin deficiency that develops in patients with long-standing diabetes.

- Started as- Single dose of long-acting insulin (0.3–0.4 U/kg per day), given either before breakfast and in the evening (NPH) or just before bedtime (NPH, glargine, detemir).
- Bedtime insulin is more effective- Since fasting hyperglycemia and increased hepatic glucose production are prominent features of type 2 DM.
- Monotherapy of type 2 DM- Insulin secretagogues, biguanides, α-glucosidase inhibitors, thiazolidinediones, GLP-1 receptor agonists, DPP-IV inhibitors, and insulin.
- Insulin secretagogues, biguanides, GLP-1 receptor agonists, and thiazolidinediones - are more effective than α-glucosidase inhibitors and DPP-IV inhibitors;
- Insulin secretagogues, GLP-1 receptor agonists, DPP-IV inhibitors, and α-glucosidase inhibitors begin to lower the plasma glucose immediately, whereas the glucose-lowering effects of the biguanides and thiazolidinediones are delayed by several weeks;
- Not all agents are effective in all individuals with type 2 DM (primary failure);
- Biguanides, α-glucosidase inhibitors, GLP-1 receptor agonists, DPP-IV inhibitors, and thiazolidinediones do not directly cause hypoglycemia.



ACUTE COMPLICATIONS OF DM-

1.Diabetic ketoacidosis

Symptoms

Nausea/vomiting Thirst/polyuria Abdominal pain Shortness of breath

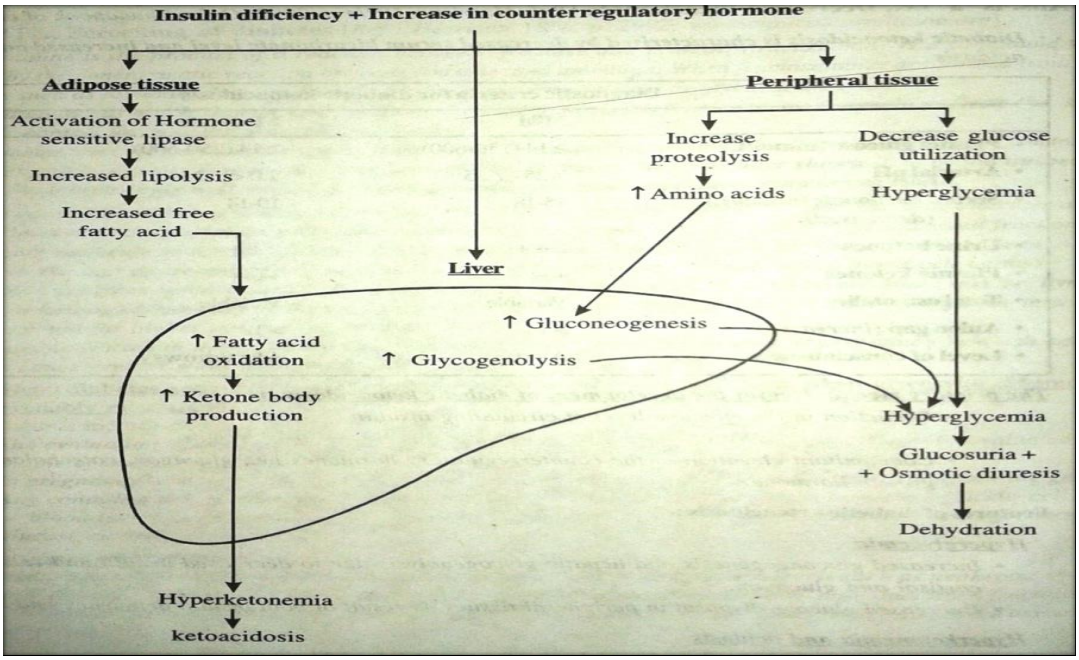
Precipitating events

- Inadequate insulin administration
- Infection (pneumonia/UTI/gastroenteritis/sepsis)
- Infarction (cerebral, coronary, mesenteric, peripheral)
- Pregnancy

Physical Findings

- Tachycardia
- Dehydration/hypotension
- Tachypnea/Kussmaul respirations/respiratory distress
- Abdominal tenderness (may resemble acute pancreatitis or surgical abdomen)
- Lethargy/obtundation/cerebral edema/possibly coma

DKA results from relative or absolute insulin deficiency combined with counterregulatory hormone excess . Both insulin deficiency and glucagon excess, and decreased ratio of insulin to glucagon promotes gluconeogenesis, glycogenolysis, and ketone body formation in the liver, as well as increases in substrate delivery from fat and muscle (free fatty acids, amino acids) to the liver. Hyperglucagonemia alters hepatic metabolism to favor ketone body formation, through activation of the enzyme carnitine palmitoyltransferase I



DKA is characterized by-

- Primary derangement-

- Hyperglycemia -Ketosis -↑Anion gap acidosis

- Secondary derangement-

  - K: Normal to ↑ - Na: Normal to ↓ - Osmolality : 300-320 mosm/ml -Leukocytosis

- Serum hydroxybutyrate is preferred over urine (by intraprusside based assay -detects acetone & acetoacetate)

Management of DKA

1.Confirm diagnosis (plasma glucose, positive serum ketones, metabolic acidosis).

2. Admit to hospital; intensive-care setting may be necessary for frequent monitoring or if pH <7.00 or unconscious.

3. Assess:

- Serum electrolytes (K^+, Na^+, Mg^{2+}, Cl^-, bicarbonate, phosphate)
- Acid-base status—pH, HCO_3^-, PCO_2, -hydroxybutyrate
- Renal function (creatinine, urine output

Management of DKA

Replace fluids:

2–3 L of 0.9% saline over first 1–3 hr

subsequently, 0.45% saline at 250–500 mL/h;

change to 5% glucose and 0.45% saline at 150–250 mL/h when plasma glucose reaches 200 mg/dL (11.2 mmol/L).

Administer short-acting insulin:

- Direct IV (0.1 units/kg),
- Then 0.1 units/kg per hour by continuous IV infusion;
- increase two- to threefold if no response by 2–4 h.
- If the initial serum potassium is <3.3 mmol/L (3.3 meq/L), do not administer insulin until the potassium is corrected.
- If the initial serum potassium is >5.2 mmol/L (5.2 meq/L), do not supplement K^+ until the potassium is corrected

K^+ replacement--

- 10 meq/h when plasma K^+< 5.0–5.2 meq/L ECG normal, urine flow and normal creatinine documented;
- administer 40–80 meq/h when plasma K^+< 3.5 meq/L.

Continue above until patient is stable, glucose goal is 8.3–13.9 mmol/L (150–250 mg/dL), and acidosis is resolved. Insulin infusion may be decreased to 0.05–0.1 units/kg per hour.

Administer long-acting insulin as soon as patient is eating. Allow for overlap in insulin infusion and SC insulin injection.

Other therapy of DKA

- Biocarbonate therapy-

Not routinely given, indicated only in cases like-

- Shock or coma •Severe acidosis • Severe hyperkalemia

- Severe depletion of buffering reserve (HOC3 <5mEq/l)
- Acidosis induced cardiac or resp. dysfunction

- Phosphate & Magnesium therapy-

2.Hyperglycemic Hyperosmolar State-

- Elderly pt with type 2 DM,
- With a several-week history of polyuria, weight loss
- Diminished oral intake that culminates in mental confusion, lethargy, or coma
- Profound dehydration and hyperosmolality and reveals hypotension, tachycardia, and altered mental status.
- Notably absent are symptoms of nausea, vomiting, and abdominal pain and the Kussmaul respirations characteristic of DKA.

Precipitated by –

- Serious, concurrent illness such as myocardial infarction or stroke.
- Sepsis, pneumonia, debilitating condition (prior stroke or dementia) or
- Social situation that compromises water intake

<u>Pathophysiology</u>

- Due to- Relative insulin deficiency and inadequate fluid intake
- Insulin deficiency-
  - Increases hepatic glucose production (through glycogenolysis and gluconeogenesis)
  - Impairs glucose utilization in skeletal muscle .
- Hyperglycemia induces an osmotic diuresis that leads to intravascular volume depletion, which is exacerbated by inadequate fluid replacement
- The absence of ketosis- due to insulin deficiency is only relative and less severe than in DKA.
- Lower levels of counter regulatory hormones and free fatty acids

- Liver is less capable of ketone body synthesis as the insulin/glucagon ratio does not favor ketogenesis.

Laboratory Abnormalities and Diagnosis-

- Marked hyperglycemia [plasma glucose may be >55.5 mmol/L (1000 mg/dL)]
- hyperosmolality (>350 mosmol/L)
- Prerenal azotemia.
- Serum sodium may be normal or slightly low
- In contrast to DKA, acidosis and ketonemia are absent or mild.
- Small anion-gap metabolic acidosis (secondary to increased lactic acid)
- Moderate ketonuria, if present, is secondary to starvation.

	DKA	HHS
Glucose[a] mmol/L (mg/dL)	13.9–33.3 (250–600)	33.3–66.6 (600–1200)
Sodium, meq/L	125–135	135–145
Potassium	Normal to low	Normal
Creatinine	Slightly increased	Moderately increased
Osmolality (mOsm/mL)	300–320	330–380
Plasma ketones	++++	+/–
Serum bicarbonate meq/L	<15 meq/L	Normal to slightly decreased
Arterial pH	6.8–7.3	>7.3
Arterial PCO_2, mmHg	20–30	Normal
Anion gap[Na – (Cl + HCO_3)]	increased	Normal to slightly increased

- **HSS Vs DKA- Pts with HHS have more-**

- Fluid losses and dehydration are usually more pronounced (d/t the prolonged illness)
- Age- Older pt,
- More likely to have mental status changes,
- Life-threatening precipitating event with accompanying comorbidities
- Higher mortality rate

Treatment--

- Fluid replacement –
  - 1–3 L of 0.9% normal saline over the first 2–3 h
  - Because the fluid deficit in HHS is accumulated over a period of days to weeks, a too rapid a reversal may worsen neurologic function.
  - If the serum sodium > 150 mmol/L (150 meq/L), 0.45% saline should be used.
  - The calculated free water deficit (which averages 9–10 L) should be reversed over the next 1–2 days (infusion rates of 200–300 mL/h of hypotonic solution).

Insulin administration--

- Insulin bolus of 0.1 units/kg followed by IV insulin at a constant infusion rate of 0.1 units/kg per hour.
- If the serum glucose does not fall, increase the insulin infusion rate by two fold.
- As in DKA, glucose should be added to IV fluid when the plasma glucose falls to 13.9–16.7 mmol/L (250–300 mg/dL), and the insulin infusion rate should be decreased to 0.05–0.1 units/kg per hour.
- The insulin infusion should be continued until the patient has resumed eating and can be transferred to a SC insulin regimen.

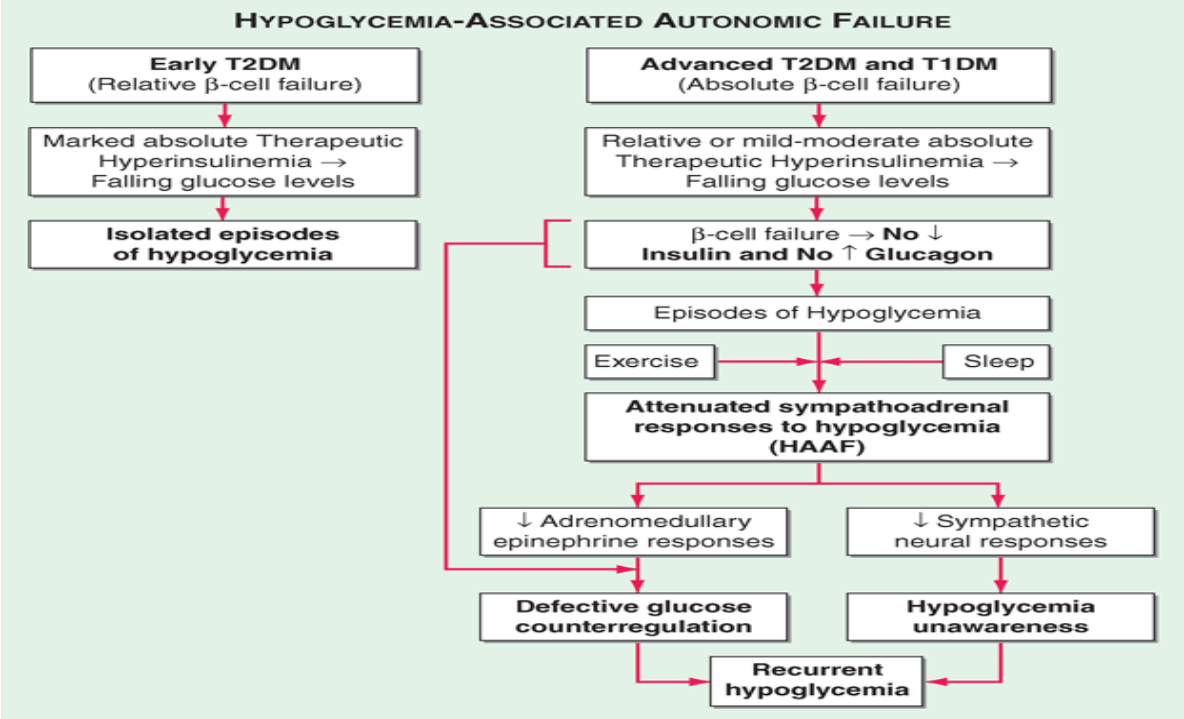
3.HYPOGLYCEMIA-

- **Common causes**
  - Missed, delayed or inadequate meal

- Unexpected or unusual exercise
- Alcohol
- Errors in OHA or insulin schedule/dose/administration
- Poorly designed insulin regimen, predisposing to nocturnal hypoglycemia

- **Common in insulin-dependent diabetics**, particularly when aggressive efforts are made to keep both the fasting plasma glucose level and postprandial hyperglycemia within the normal range.
- **Symptoms-**
  - Daytime episodes -Autonomic symptoms, such as sweating, nervousness, tremor, and hunger.
  - Hypoglycemia during sleep -no symptoms or cause night sweats, unpleasant dreams, and early-morning headache.
- **Hypoglycemia is prevented by two mechanisms:**
  - Cessation of insulin release
  - Mobilization of counterregulatory hormones.
    - Glucagon is the primary counterregulatory hormone,
    - Epinephrine and norepinephrine (serve as the major backup)
    - Cortisol and GH- play in prolonged fasting or sustained hypoglycemia.

HAAF in diabetes posits that recent antecedent iatrogenic hypoglycemia causes both defective glucose counterregulation (by reducing the epinephrine response to a given level of subsequent hypoglycemia in the setting of absent insulin and glucagon responses) and hypoglycemia unawareness (by reducing the sympathoadrenal response to a given level of subsequent hypoglycemia). Reversible by as little as 2–3 weeks of scrupulous avoidance of hypoglycemia in most affected patients.



Treatment-

- Conscious pt- sugar-containing eatables (however, this is ineffective orally if patient is receiving acarbose)
- Unconscious pt-
  - IV glucose is required (*100 ml of 25% dextrose)*
  - Administration of *1 mg glucagon IM*
- Recurrence should be anticipated-
  - When patient using long-acting insulin or sulfonylureas,
  - Such patients should be admitted.
- Cerebral edema –
  - Occurs in patients who fail to regain consciousness after blood glucose is restored to normal.

- It has high mortality and morbidity, and required **urgent treatment with mannitol and high –dose oxygen.**

Chronic Complications of Diabetes Mellitus	
Microvascular	**Other**
Eye disease	Gastrointestinal (gastroparesis, diarrhea)
Retinopathy (nonproliferative/proliferative)	Genitourinary (uropathy/sexual dysfunction)
Macular edema	Dermatologic
Neuropathy	Infectious
Sensory and motor (mono- and polyneuropathy)	Cataracts
Autonomic	Glaucoma
Nephropathy	Periodontal disease
Macrovascular	Hearing loss
Coronary heart disease	
Peripheral arterial disease	
Cerebrovascular disease	

Mechanisms of Complications-

<u>Four prominent theories-</u>

Mechanisms of Hyperglycemia-Induced Damage

Four major hypotheses about how hyperglycemia causes diabetic complications

Increased Polyol Pathway Flux

Increased Intracellular Formation of Advanced Glycation End Products

Activation of Protein Kinase C

Increased Hexosamine Pathway Flux

The details of polyol pathway are shown below.

Aldose reductase and the polyol pathway.

Aldose reductase reduces reactive oxygen species (ROS)-generated toxic aldehydes to inactive alcohols, and glucose to sorbitol, using triphosphopyridine nucleotide (NADPH), the reduced form of nicotinamide adenine dinucleotide phosphate (NADP), as a cofactor. In cells in which aldose reductase activity is sufficient to deplete reduced glutathione (GSH), oxidative stress would be augmented. Sorbitol dehydrogenase (SDH) oxidizes sorbitol to fructose using nicotinamide-adenine dinucleotide (NAD+) as a cofactor. GSSG, oxidized

glutathione.

Ophthalmologic Complications of Diabetes Mellitus-

- Acute hyperglycemia -Induce sudden myopia because of fluid imbibition & swelling of lens
- Diabetic retinopathy : two stages: nonproliferative and proliferative.

Nonproliferative diabetic retinopathy-

- Appears late in the first decade or early in the second decade of the disease and is marked by

• Retinal vascular microaneurysms, (earliest) • Blot hemorrhages •Cotton-wool spots

- Blindness in nonproliferative retinopathy is cause by macular edema.
- Fluorescein angiography is useful to detect macular edema

Proliferative diabetic retinopathy

- **Neovascularization** in response to retinal hypoxemia
    - Vessels appear near the optic nerve and/or macula and rupture easily,
    - Leading to **vitreous hemorrhage, fibrosis, and ultimately retinal detachment.**
- **Retinal detachment** - MC cause of blindness in proliferative retinopathy.
- Only more severe nonproliferative disease- develop to proliferative retinopathy in 5 yr
- Duration of DM and degree of glycemic control are the best predictors

- Rubeosisiridis and neovascular glaucoma- d/t Neovascularisation in extending to iris

Treatment-

- Proliferative retinopathy is usually treated – **Panretinal laser photocoagulation**
- Macular edema is treated with **focal laser photocoagulation.**
- Aspirin therapy **does not** alter the natural history of diabetic retinopathy.
- **Bevacizumab** (anti-VEGF), into the eye has been shown to stop the growth of the new blood vessels in diabetic eye disease.

SCREENING – for diabetic retinopathy-

TYPE-2 D.M

- Long asymptomatic periods before they are diagnosed.
- Screening (fundal examination) should be done at the time of diagnosis.
- If no abnormality is detected , 6 monthly or annual review is recommended.

TYPE-1 D.M-

- Acute onset , no asymptomatic stage
- Hence, Screened 5 years after the onset of diabetes and reviewed yearly thereafter.

Diabetic nephropathy

- Leading cause of ESRD and DM-related morbidity and mortality.
- increased risk of :
    - Cardiovascular disease.
    - Diabetic retinopathy.
- Pathogenesis is related to chronic hyperglycemia

Glomerular hyperperfusion and renal hypertrophy-

- Occur in the first years after the onset of DM
- Associated with an increase of the GFR

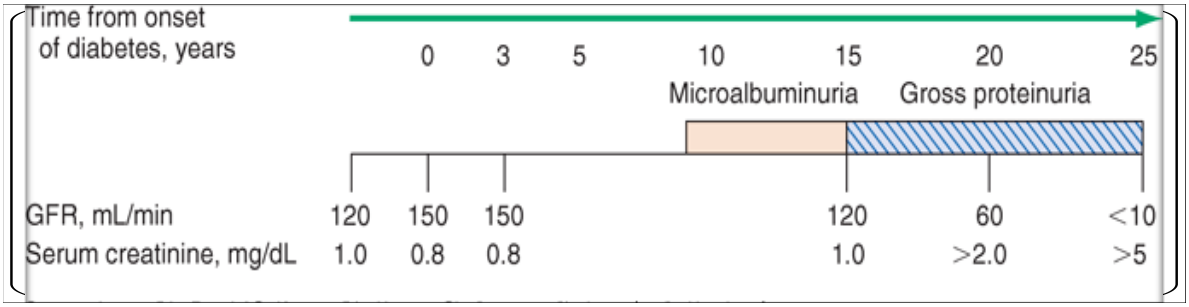
- During the first 5 years of DM-
    - Thickening of The Glomerular Basement Membrane,
    - Glomerular Hypertrophy
    - Mesangial volume expansion occur as the GFR returns to normal.
- After 5–10 years of type 1 DM-
    - 40% of individuals begin to excrete small amounts of albumin in the urine.

Microalbuminuria is defined as-

- 30–299 mg/d in a 24-h collection or 30–299 g/mg creatinine in a spot collection.

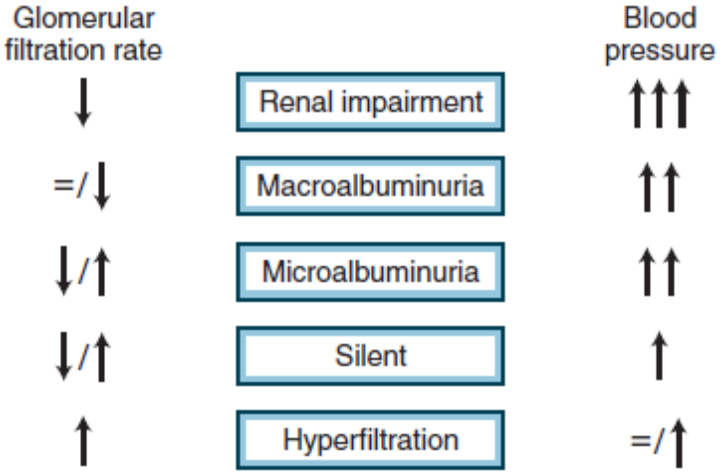
- Macroalbuminuria -50% of individuals with type 1 DM with microalbuminuria -progress to macroalbuminuria (>300 mg/d or > 300 g/mg creatinine) in10 yr

- Once macroalbuminuria is present-
    - Steady decline in GFR, and 50% of individuals reach ESRD in 7–10 years.
    - Blood pressure rises slightly
    - Pathologic changes are likely irreversible.



STAGES OF DIABETIC NEPHROPATHY: (IDDM)

Year	Stage	Findings
0	I	• Raised GFR, increase in Renal size and plasma flow
2	II	• Thickening in glomerular capillary basement membrane
6-10	III	• Microalbuminuria/Albumin excretion rate 30-300mg/day, Appearance of micro albuminuria important predictor of development of overt proteinur
10-15	IV	• Clinical nephropathy, gross proteinuria, Albumin>300mg/day. Now the changes are irreversible
16-25	V	• End stage renal disease



Pathology of diabetic nephropathy

- Capillary basement membrane thickening
- Diffuse mesangial matrix (PAS +ve)
- Nodular glomerulosclerosis

-Intercapillary Nodular glomerulosclerosis - Or Kimmelsteil Wilson disease

Treatment

- Modest restriction of protein intake-

-Microalbuminuria (0.8–1.0 g/kg per day) - Macroalbuminuria (<0.8 g/kg per day).

- Medications-

- ACE inhibitors
- ARBs is

-Calcium channel blockers (non-dihydropyridine class)
-Beta blockers,

- Transplantation –

- Renal transplantation -Combined pancreas-kidney transplant - Diuretics

Methods to halt progression of microalbuminuria to overt proteinuria

• Near normalization of hyperglycemia • Strict BP control

• ACE-I & ARBs • T/t of dyslipidemia

Diabetes Neuropathy

- Occurs in **approximately 50%.**
- Correlates with the **duration of diabetes and glycemic control.**
- **Manifest as** polyneuropathy, mononeuropathy, and/or autonomic neuropathy.
- **Distal symmetric polyneuropathy-** MC form of diabetic neuropathy .
- MC symptom- distal sensory loss.
- Hyperesthesia, paresthesia, and pain also occur.
- Physical examination reveals *sensory loss, loss of ankle reflexes, and abnormal position sense*.
- Neuropathic pain- Involves the lower extremities, present at rest & worsens at night
- As diabetic neuropathy progresses, the pain subsides and **eventually disappears**, and a sensory deficit in the lower extremities persists.

- Long-term complications include-

- Insensitivity of the feet - Leading to repeated 'silent' trauma

- Predisposes to **neuropathic plantar ulcers or deformities of the feet secondary to multiple silent fractures** (**charcot's joint**).

Diabetic polyradiculopathyis a syndrome characterized by-

- Severe disabling pain in the distribution of one or more nerve roots.
- Accompanied by motor weakness.
- *Intercostal or truncal radiculopathy* causes pain over the thorax or abdomen.
- *Lumbar plexus or femoral nerve* Involvement –
    - May cause pain in the thigh or hip
    - May be associated with muscle weakness in the hip flexors or extensors (**diabetic amyotrophy**).
- **Self-limited and resolve over 6 to 12 months.**

Mononeuropathy -

- Presents with spontaneous reversible pain and motor weakness along a single nerve.
- MC cranial nerve Involvement - Third cranial nerve & may lead to diplopia.
- Ptosis and opthalmoplegia with normal papillary constriction to light.
- Sometimes cranial nerves IV, VI, or VII (Bell's palsy) are affected.
- Peripheral mononeuropathies or simultaneous involvement of more than one nerve (mononeuropathy multiplex) may also occur.

Autonomic Neuropathy

- **Affect CVS- Cause***resting tachycardia and orthostatic hypotension*.and sudden death.
- **Gastroparesis and bladder-emptying abnormalities** are also likely related to the autonomic neuropathy seen in DM.

- **Hyperhidrosis of the upper extremities and anhidrosis of the lower extremities** result from sympathetic nervous system dysfunction.
- Increases the risk of skin ulceration- Anhidrosis can promote dry skin with cracking.
- May reduce counterregulatory hormone release, leading to-
    - Inability to sense hypoglycemia appropriately (**hypoglycemia unawareness**),
    - Risk of severe hypoglycemia and complicating efforts to improve glycemic control.

Treatment-

- **Avoidance of neurotoxins** (alcohol),
- **supplementation with vitamins** for possible deficiencies (B12, B6, Folate),

<u>Symptomatic treatment-</u>

- Precautions (footwear) aimed at preventing calluses or ulcerations.
- Chronic, painful diabetic neuropathy is **difficult to treat** but may respond to –
    - Antidepressants (amitriptyline, duloxetine) or
    - Anticonvulsants (gabapentin, carbamazepine, lamotrigine).
- **Duloxetine and pregabalin**, - pain associated with diabetic neuropathy.
- **Orthostatic hypotension- treated** with fludrocortisone, midodrine, clonidine, octreotide, and yohimbine
- Nonpharmacologic maneuvers (adequate salt intake, avoidance of dehydration and diuretics, and lower extremity support hose) may offer some benefit.

GASTROINTESTINAL/GENITOURINARY DYSFUNCTION

- MC GIT symptoms –
    - Delayed gastric emptying (gastroparesis)
    - Altered small- and large-bowel motility (constipation or diarrhea).

- MC Genitourinary symptoms –
    - Prouce cystopathy,
    - Erectile dysfunction in male
    - Female sexual dysfunction (reduced sexual desire, dyspareunia, reduced vaginal lubrication)

Treatment-

- Smaller, more frequent meals ,
- Dopamine antagonists (metoclopramide, and domperidone,)before each meal,
- Erythromycin .

- Diabetic diarrhoea-
    - Loperamide, octreotide - Treatment of bacterial overgrowth with antibiotics .
- Diabetic cystopathy-
    - timed voiding or self-catherization - Bethanechol.
- The drug of choice for erectile dysfunction is sildenafil, *vardenafil and tadalafil.*

CARDIOVASCULAR COMPLICATIONS-

- Increased in individuals with type 1 or type 2 DM.
- DM is a **major risk factor** for cardiovascular disease
- **Cardiac stress test-** should be sought in the individual with diabetes who:
    - Has symptoms suggestive of cardiac ischemia
- A resting electrocardiogram indicative of prior infarction
- Two other cardiac risk factors
    - Proteinuria, or - Plans to initiate an exercise program (ADA recommendations).

- **Stroke** is increased in individuals with DM (threefold increase)
- Increased incidence of **congestive heart failure** (diabetic cardiomyopathy).

Primary prevention-

- **Antiplatelet therapy should be strongly considered**,
    - *>30 years of age*
    - *Other coronary risk factors such as hypertension, smoking, family history or dyslipidemia.*

Secondary prevention- ACE inhibitors (or ARBs), beta blockers , aspirin

Dyslipidemia-

- MC **pattern** of dyslipidemia**-**
    - *Hypertriglyceridemia*
    - *Reduced HDL cholesterol* levels,
    - *Small dense LDL particles.*

Target lipid values in diabetic (age >40 years) **without cardiovascular disease**(primary prevention) should be-

- LDL < 100 mg/dL
- HDL > 40 mg/dL in men and >50 mg/dL in women, and
- Triglycerides < 150 mg/dL.
- In diabetic individuals **with cardiovascular disease**, the LDL goal is < 70 mg/dL.
- Above 40 years- Add **statin** , regardless of the LDL.
- **The target** for BP control is-

- <130/80 in diabetics - <125/75 in diabetics with macroalbuminuria.

- **Diabetes and hypertension by treated with-**
    - **ACE inhibitor or ARB.**

- *Subsequently,* agents that reduce cardiovascular risk (beta lockers, thiazide diuretics, and calcium channel blockers) should be incorporated into the regimen.
- Non-dihydropyridine calcium channel blockers (**verapamil and diltiazem)- preferred**

SCREENING IN DIABETICS-

- Screening for **dyslipidemia and hypertension** - performed annually.
- An annual **comprehensive eye examination-**

ADA recommends:

- Individuals with type 1 DM- initial examination within 3-5 yrs of diagnosis,
- Individuals with type 2 DM- initial examination at the time of diabetes diagnosis,
- Individuals normal- repeat examination in 2-3 years

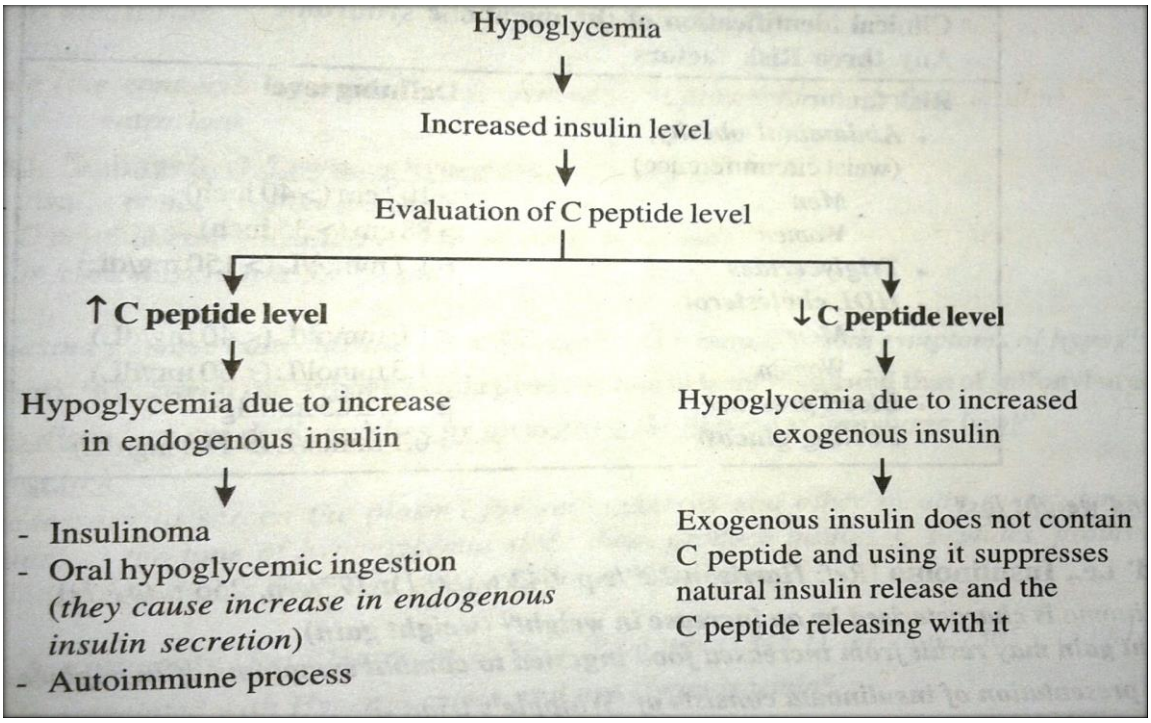
An **annual foot examination** should:

- (1) assess blood flow, sensation (monofilament, pin prick or tuning fork), and nail care;
- (2) foot deformities such as hammer or claw toes and Charcot foot; and
- (3) sites of potential ulceration..
- An **annual microalbuminuria measurement** is advised in individuals with type 1 or type 2 DM and no protein on a routine urinalysis.
- *Screening should commence* 5 years after the onset of type 1 DM and at the time of onset of type 2 DM.
- Regardless of protein excretion results, the GFR should be estimated using the **serum creatinine in all patients on an annual basis**.

Guidelines for Ongoing Medical Care for Patients with Diabetes
Self-monitoring of blood glucose (individualized frequency)
A1C testing (2–4 times/year)
Patient education in diabetes management (annual)
Medical nutrition therapy and education (annual)
Eye examination (annual)
Foot examination (1–2 times/year by physician; daily by patient)
Screening for diabetic nephropathy (annual)
Blood pressure measurement (quarterly)
Lipid profile and serum creatinine (estimate GFR) (annual)
Influenza/pneumococcal immunizations
Consider antiplatelet therapy , aspirin therapy should be considered in many patients with diabetes (primary prevention in type 1 or type 2 DM men >50 years or women >60 years with one risk factor CV disease.

Causes of Hypoglycemia in Adults

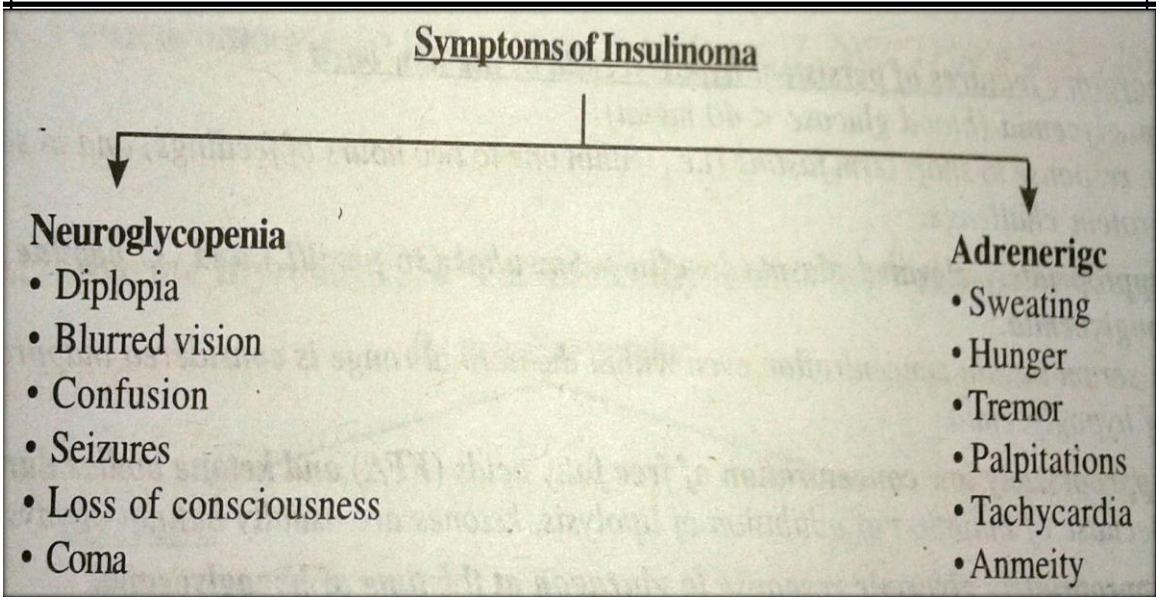
Ill or medicated individual	Seemingly well individual
1. Drugs	5. Endogenous hyperinsulinism
Insulin or insulin secretagogue	Insulinoma
Alcohol	Functional beta-cell disorders (nesidioblastosis)
Others	Noninsulinoma pancreatogenous hypoglycemia
2. Critical illness	Post–gastric bypass hypoglycemia
Hepatic, renal or cardiac failure	Insulin autoimmune hypoglycemia
Sepsis	Antibody to insulin
Inanition	Antibody to insulin receptor
3. Hormone deficiency	Insulin secretagogue
Cortisol	Other
Glucagon and epinephrine (in insulin-deficient diabetes)	6. Accidental, surreptitious or malicious hypoglycemia
4. Non–islet cell tumor-Fibrosarcoma, etc.	



Interpretation of C peptide level

- ***Undetectable C peptides with high blood glucose indicates***
  - *Type I diabetes (insulin is not released)*
- ***High level of both C peptide and blood glucose are present***
  - *Type 2 diabetes or insulin resistance is likely (insulin resistance)*
- ***High level of C peptide with a low blood glucose level may indicate :-***
  - *Insulinoma*
  - *α pancreatic tumour producing excess insulin*
  - *Certain medications such as sulfonylureas or meglitinides. (They cause increase in endogenous insulin secretion)*
- ***Low blood sugar and low C peptide level***
  - *Excessive use of exogenous insulin*
  - *Liver disease*
  - *Severe infection*
  - *Addison's disease*

Insulinoma



- More than 90% are benign,
- Age-50 years in sporadic cases,
- Third decade –as a component of MEN-1

Whipple's triad-

- Symptoms of hypoglycemia
- FBS <50mg%
- Symptoms relieved by taking oral/ IV glucose

Diagnosis

- Insulinoma is assessed by measuring-
  - Plasma insulin
  - C peptide
  - Glucose conc.
- Critical diagnostic findings in endogenous hyperinsulinism-
  - Plasma insulin ≥ 3μ/ml
  - Plasma C peptide ≥ 6ng/ml
  - Proinsulin conc ≥ 5 p.mol/L

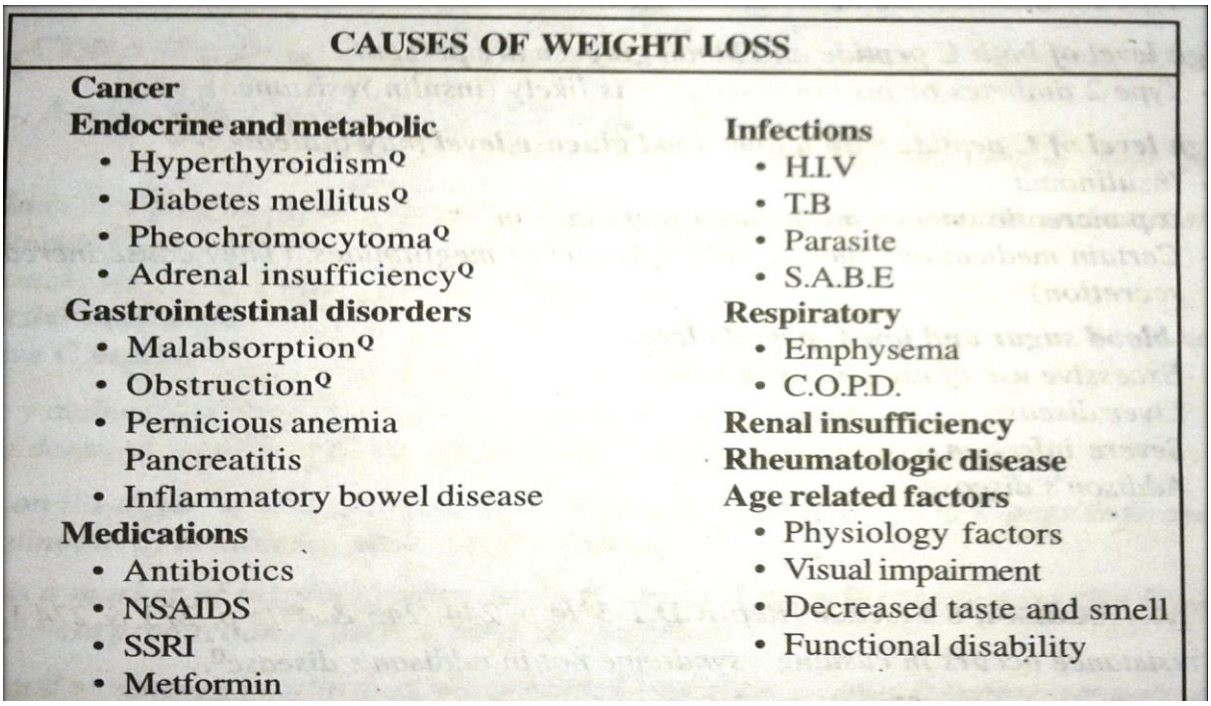
Recent investigations

- CT or MRI detects approximately 70–80% of insulinomas
- Transabdominal ultrasound

- Endoscopic ultrasound –sensitivity 90%
- Somatostatin receptor scintigraphy
- Selective pancreatic arterial calcium injections
- Intraoperative pancreatic ultrasonography

Treatment

- Surgical resection of a solitary insulinoma is generally curative.
- Medical-
  - Diazoxide, which inhibits insulin secretion, or
  - Somatostatin analogue octreotide can be used to treat hypoglycemia in patients with unresectable tumors;
  - Everolimus, an mTOR (mammalian target of rapamycin) inhibitor



CAUSES OF WEIGHT LOSS

Cancer

Endocrine and metabolic
- Hyperthyroidism^{Q}
- Diabetes mellitus^{Q}
- Pheochromocytoma^{Q}
- Adrenal insufficiency^{Q}

Gastrointestinal disorders
- Malabsorption^{Q}
- Obstruction^{Q}
- Pernicious anemia
  Pancreatitis
- Inflammatory bowel disease

Medications
- Antibiotics
- NSAIDS
- SSRI
- Metformin

Infections
- H.I.V
- T.B
- Parasite
- S.A.B.E

Respiratory
- Emphysema
- C.O.P.D.

Renal insufficiency

Rheumatologic disease

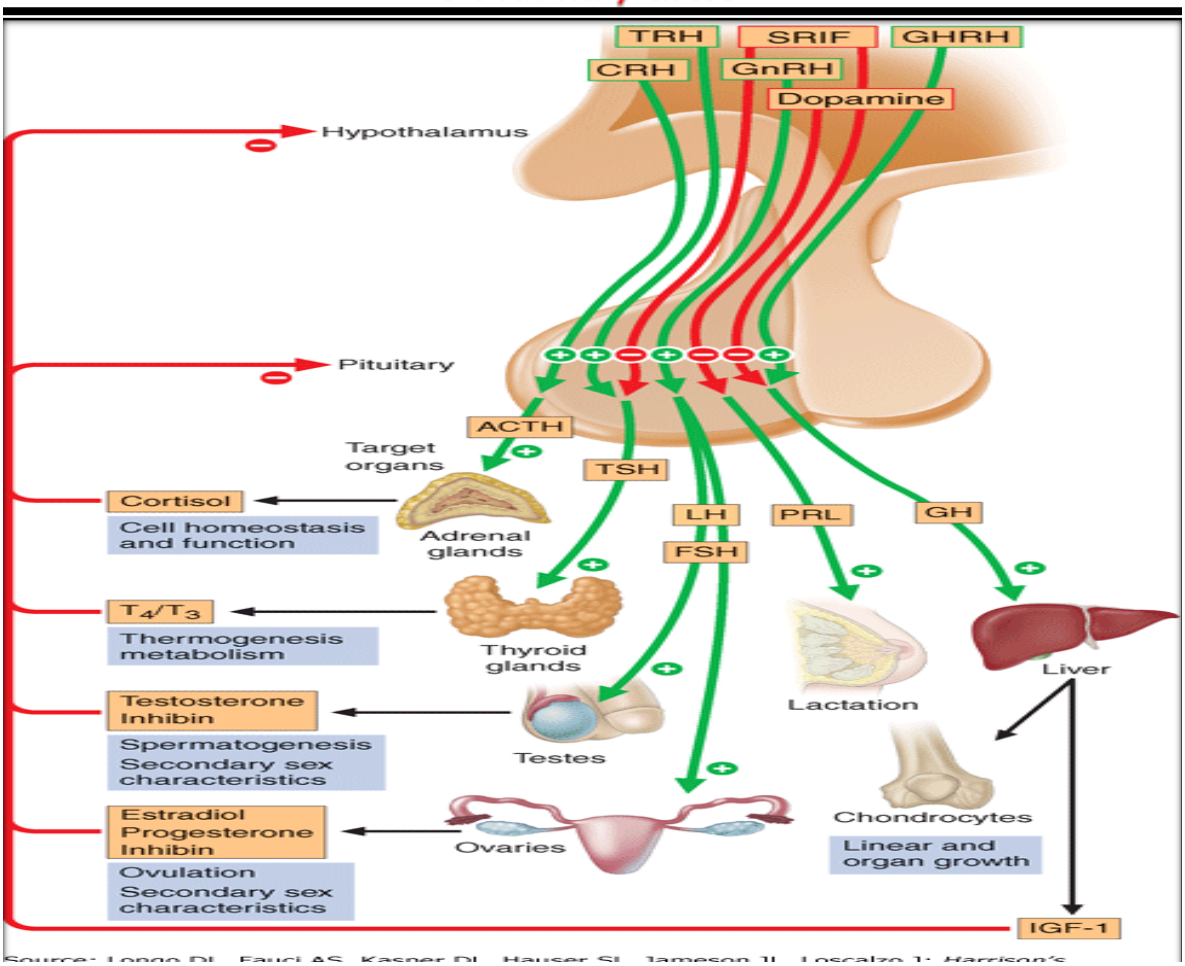
Age related factors
- Physiology factors
- Visual impairment
- Decreased taste and smell
- Functional disability

Pituitary and Adrenal Gland

Anterior Pituitary

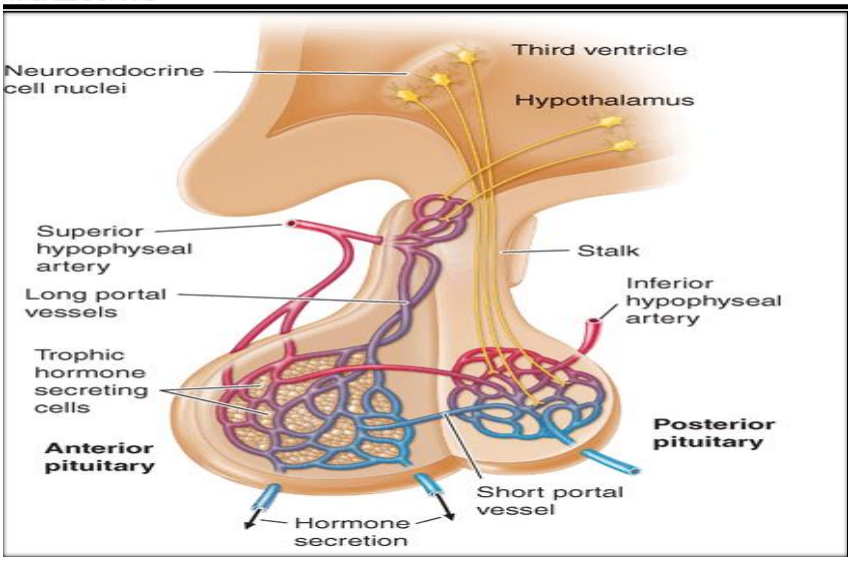
Cell	Corticotrope	Somatotrope	Lactotrope	Thyrotrope	Gonadotrope
Hormone	POMC	GH	PRL	TSH	FSH LH
Protein	Polypeptide	Polypeptide	Polypeptide	Glycoprotein , subunits	Glycoprotein , subunits
Stimulators	CRH, AVP	GHRH, ghrelin	Estrogen, TRH	TRH	GnRH, activins, estrogen
Inhibitors	Glucocorticoids	Somatostatin, IGF-I	Dopamine	T_3, T4, dopamine, somatostatin, glucocorticoid	Sex steroids, inhibin
Target gland	Adrenal	Liver, other tissues	Breast, other tissues	Thyroid	Ovary, testis
Trophic effect	Steroid production	IGF-I production, growth induction, insulin antagonism	Milk production	T4 synthesis and secretion	Sex steroid production, follicle growth, germ cell maturation
Normal range	ACTH, 4–22 pg/L	<0.5 g/μL*	M < 15; F <20μ g/L	0.1–5 mU/L	M, 5–20 IU/L, F (basal), 5–20 IU/L

Pituitary axis



Hypothalamo-pituitary vasculature

Interruption of the pituitary stalk –reduction in release of GH, LH, FSH, TSH & ACTH, increase of PRL



Hypopituitarism

Development/structural
Transcription factor defect
Pituitary dysplasia/aplasia
Congenital CNS mass, encephalocele
Primary empty sella
Congenital hypothalamic disorders (septo-optic dysplasia,
Prader-Willi syndrome, Laurence-Moon-Biedl syndrome,
Kallmann syndrome)
Traumatic
Surgical resection
Radiation damage & Head injuries
Neoplastic
Pituitary adenoma
Parasellar mass (germinoma, ependymoma, glioma)
Rathke's cyst
Craniopharyngioma
Hypothalamic hamartoma, gangliocytoma
Pituitary metastases (breast, lung, colon carcinoma)
Lymphoma and leukemia

Infiltrative/inflammatory
Lymphocytic hypophysitis
Hemochromatosis
Sarcoidosis
Histiocytosis X
Granulomatous hypophysitis
Vascular
Pituitary apoplexy
Pregnancy-related (infarction with diabetes; postpartum necrosis)
Sickle cell disease
Arteritis
Infections
Fungal (histoplasmosis)
Parasitic (toxoplasmosis)
Tuberculosis
Pneumocystis carinii

Clinical manifestations –

Depend on which hormones are lost and the extent of such loss.

A. GH deficiency causes –

- growth disorders in children
- abnormal body composition in adults.

B. Gonadotropin deficiency causes –

- infertility and menstrual irregularity in women
- decreased sexual functions in men.

C. TSH deficiency leads to-

- Growth retardation in children
- Features of hypothyroidism in children and in adults.

D. ACTH deficiency leads to -

- Hypocortisolism
- Relative preservation of mineralocorticoid production.

E. TSH and ACTH deficiency usually develop later in the course of pituitary failure.

F. PRL deficiency leads to failure of lactation.

- Pituitary failure usually occurs in a specific sequence - **GH>FSH>LH>TSH>ACTH**.
- Thus during childhood, *growth retardation* is the usual presenting feature
- In adults, *hypogonadism* is the earliest symptom

Kallmann syndrome results from -

- *Defective hypothalamic GnRH synthesis,*
- *Anosmia* due to olfactory bulb agenesis or hypoplasia.
- MC cause of congenital isolated gonadotropin deficiency.

Laurence-Moon-Biedlsyndrome -

- Central hypogonadism (GnRH deficiency, mental retardation, obesity

- *Finger abnormalities* (hexadactyly, syndactyly or brachydactyly)

Prader-Willi syndrome-

Central hypogonadism, Mental retardation

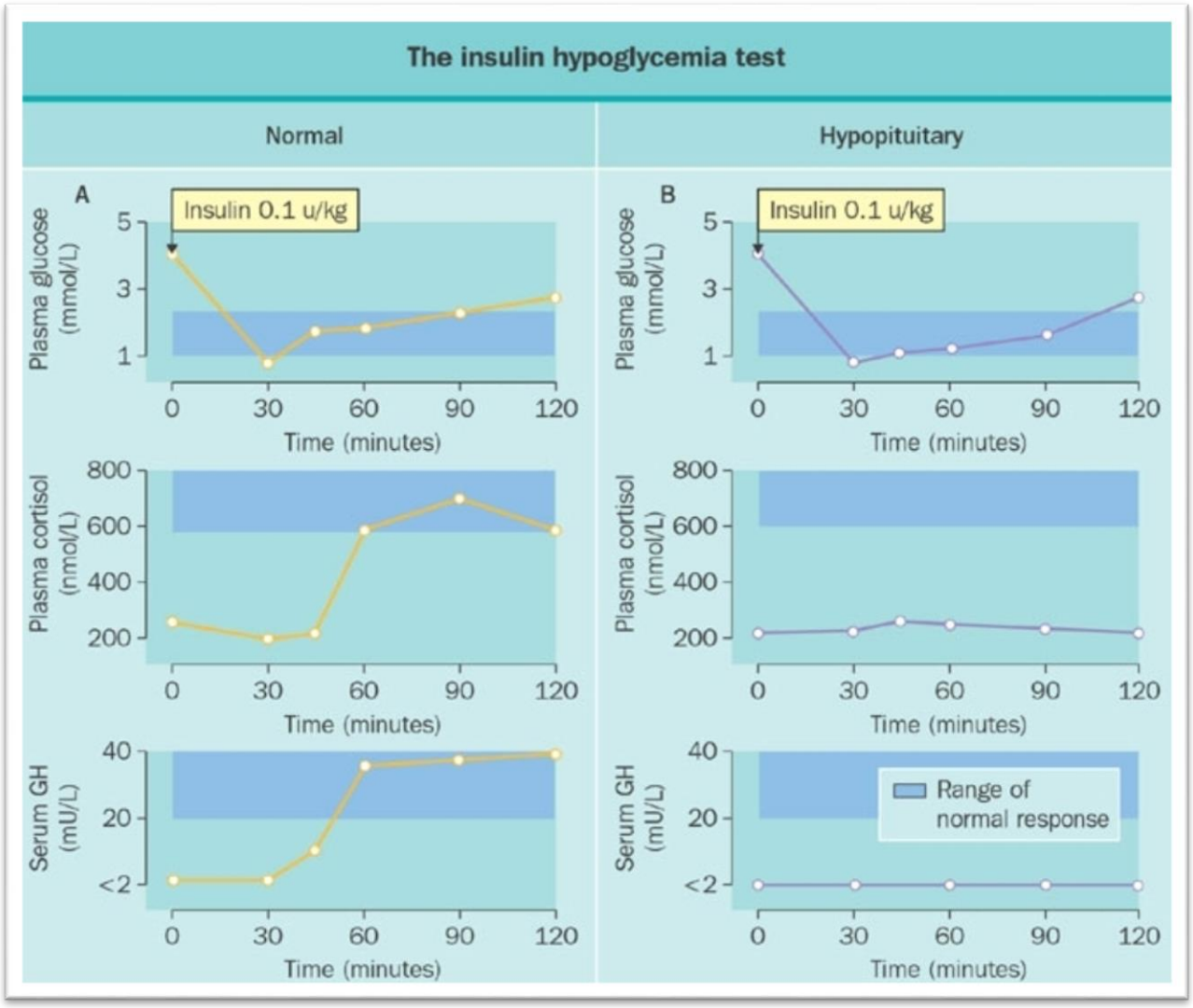
Obesity *Chronic muscle hypotonia*
Adult onset diabetes.

<u>Inflammatory (lymphocytic hypophysitis</u>)

- Characterized by **pituitary failure due to diffuse lymphocytic infiltration**.
- Hypopituitarism may be *transient or permanent*, and occurs mainly in **postpartum women**.
- **symptoms of progressive mass effects** with headache and visual disturbance.
- There is usually mild elevation of serum prolactin levels, and ESR is often elevated.
- **MRI shows evidence of a prominent pituitary mass resembling an adenoma**.
- Resolves with several months of **glucocorticoid treatment** and pituitary function may be restored, depending on the extent of damage.

Laboratory Investigation- Hypopituitarism

- By demonstrating low levels of trophic hormones in the setting of low levels of target hormones.
    - For example, low free thyroxine in the setting of a low or inappropriately normal TSH level suggests secondary hypothyroidism
    - Similarly, a low testosterone level without elevation of gonadotropins suggests hypogonadotropic hypogonadism.
- **Provocative tests -** required to assess pituitary reserve Ex—
    - GH responses to insulin-induced hypoglycemia, arginine, l-dopa, growth hormone–releasing hormone (GHRH).
    - Corticotropin-releasing hormone (CRH) administration induces ACTH release, and



- administration of synthetic ACTH (cosyntropin) evokes adrenal cortisol release as an indirect indicator of pituitary ACTH reserve

Tests of Pituitary Sufficiency

Hormone	Test
Growth hormone	Insulin tolerance test, GHRH test, L–Arginine test, L–Dopa test
ACTH	Insulin tolerance test, CRH test, Metyrapone test, Standard ACTH stimulation test
TSH	Basal thyroid function tests: T4, T_3, TSH, TRH stimulation test
LH, FSH	Basal LH, FSH, testosterone, estrogen, GnRH stimulation test

Pituitary Apoplexy

Ac intrapituitary hemorrhagic vascular event causing substantial damage

Symptoms:

- Endocrine mergency
  - Severe hypoglycemia
  - Hypotension
  - CNS hemorrhage & death
- Acute symptoms-
  - Severe headache & meningeal irritation
  - b/l visual loss
  - Ophthalmoplegia
  - CVS collapse & loss of consciousness (In severe cases)

Causes-

- Infarction in Pre-exisiting adenoma
- Postpartum (Sheehan's synd.)
- DM
- HTN
- Sickle cell anemia
- Acute shock

Diagnosis-

- CT / MRI – shows intratumoral or sellar hemorrhage with deviation of pituitary stalk and compression of pituitary tissue

Treatment-

- No visual loss- conservative t/t, steroids
- With visual loss- surgery

Hormone Replacement Therapy for Hypopituitarism	
ACTH	Hydrocortisone (10-15 mg/m^2/day, 10–20 mg A.M.; 5–10 mg P.M.) Prednisone (5 mg A.M.)
TSH	Levothyroxine (1.6–1.8 mcg/kg/day)
FSH/LH	Males Testosterone enanthate (200 mg IM every 2 weeks) Testosterone skin patch (5 mg/d) Females Conjugated estrogen (0.65–1.25 mg qd for 25 days) Progesterone (5–10 mg qd) on days 16–25 Estradiol skin patch (0.5 mg, every other day) For fertility: Menopausal gonadotropins, human chorionic gonadotropins
GH	Adults: Somatotropin (100-300mcg per day) Children: Somatotropin [0.02–0.05 (mg/kg per day)]
Vasopressin	Intranasal desmopressin (5–20µg twice daily) Oral 300–600 µg qd

Sellar Mass Lesions		
Classification of Pituitary Adenomas		
Adenoma Cell Origin	**Hormone**	**Clinical Syndrome**
Lactotrope	PRL	Hypogonadism, galactorrhea
Gonadotrope	FSH, LH,	Silent or hypogonadism
Somatotrope	GH	Acromegaly/gigantism
Corticotrope	ACTH	Cushing's disease
Mixed growth hormone and prolactin cell	GH, PRL	Acromegaly, hypogonadism, galactorrhea
Other plurihormonal cell	Any	Mixed

Lab investigation

Initial hormonal evaluation –

(When a pituitary adenoma is suspected based on MRI)

- (1) basal PRL;
- (2) insulin-like growth factor (IGF)- I;
- (3) 24-h urinary free cortisol (UFC) and/or overnight oral dexamethasone (1 mg) suppression test;
- (4) subunit, FSH, and LH;
- (5) thyroid function tests.

Screening Tests for Functional Pituitary Adenomas		
	Test	Comments
Acromegaly	Serum IGF-I	Interpret IGF-I relative to age- and sex-matched controls
	Oral glucose tolerance test with GH obtained at 0, 30, and 60 min	Normal subjects should suppress growth hormone to <1 g/L
Prolactinoma	Serum PRL	Exclude medications
		MRI of the sella should be ordered if prolactin is elevated
Cushing's disease	24-h urinary free cortisol	Ensure urine collection is total and accurate
	Dexamethasone (1 mg) at 11 P.M. and fasting plasma cortisol measured at 8 A.M.	Normal subjects suppress to <5 g/dL
	ACTH assay	Distinguishes adrenal adenoma (ACTH suppressed) from ectopic ACTH or Cushing's disease (ACTH normal or elevated)

Treatment

1. Trans-sphenoidal resection
2. Radiotherapy
3. Medication - highly specific and depends on tumor type.
    i. Prolactinomas- dopamine agonists
    ii. Acromegaly -somatostatin analogues and GH receptor antagonists
    iii. TSH-secreting tumors- somatostatin analogues and dopamine agonists
    iv. ACTH-secreting tumors and nonfunctioning tumors -require surgery and/or irradiation

Features of other Sellar Mass Lesions

Impacted Structure	Clinical Impact
Pituitary	Hypogonadism Hypothyroidism Growth failure and adult hyposomatotropism Hypoadrenalism,Hyperprolactinoma
Optic chiasm	Loss of red perception Bitemporal hemianopia Superior or bitemporal field defect Scotoma Blindness
Hypothalamus	Temperature dysregulation Appetite and thirst disorders Obesity Diabetes insipidus Sleep disorders Behavioral dysfunction Autonomic dysfunction

Impacted Structure	Clinical Impact
Cavernous sinus	Opthalmoplegia with or without ptosis or diplopia Facial numbness
Frontal lobe	Personality disorder Anosmia
Brain	Headache Hydrocephalus Psychosis Dementia Laughing seizures

Diagnosis-

- Clinically silent sellar mass - laboratory studies needed for
  - determining **the nature of the tumor**
  - assessing the possible presence **of hypopituitarism.**
- **Sagittal and coronal T1-weighted MRI imaging-**
  - **A**llows precise visualization of the pituitary gland with clear delineation of the hypothalamus, pituitary stalk, pituitary tissue and surrounding suprasellar cisterns, cavernous sinuses, sphenoid sinus, and optic chiasm.

- Visual field assessment using perimetry – needed for patients with sellar mass lesions present near optic chiasma

Treatment–

- **Transsphenoidal surgery**
- **Stereotactic radiotherapy (including gamma-knife radiotherapy**),
- HRT if Hypopituitarism occurs.

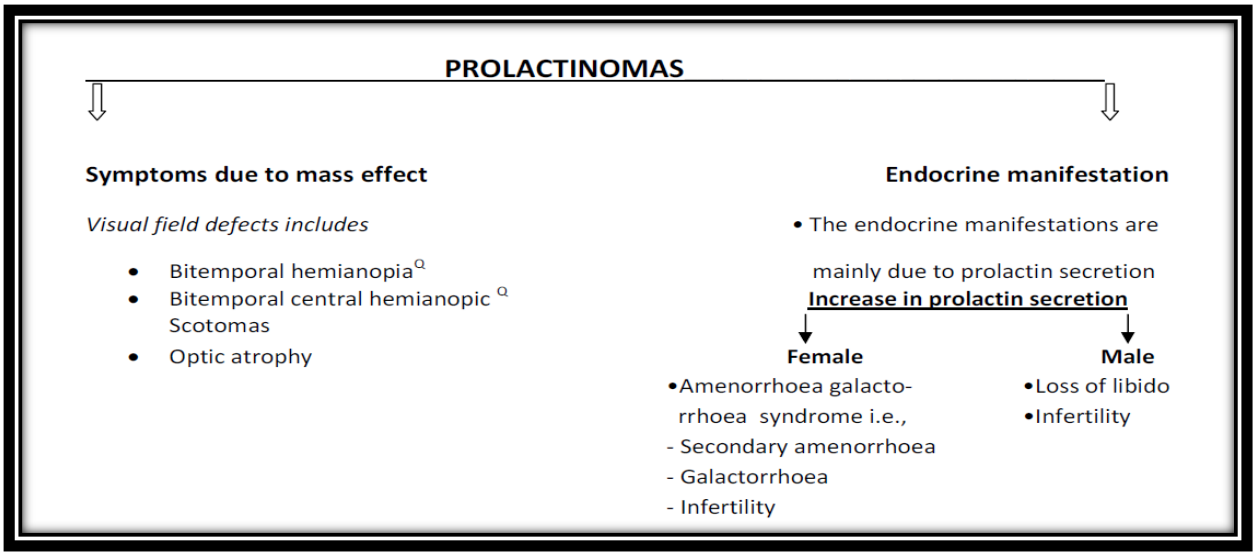
Prolactin

- Normal adult serum PRL levels –
  - 10–25 µg/L in women
  - 10–20 µg/L in men
- Pulsatile – Peak with rapid eye movement sleep
- Action-
  - Induce and maintain lactation,
  - Decrease reproductive function,
  - Suppress sexual drive

Etiology of Hyperprolactinemia	
I. Physiologic hypersecretion •Pregnancy and Lactation •Chest wall stimulation •Sleep and Stress	**III. Pituitary hypersecretion** •Prolactinoma •Acromegaly
II. Hypothalamic–pituitary stalk damage •Tumors •Empty sella •Lymphocytic hypophysitis •Adenoma with stalk compression •Granulomas •Rathke's cyst •Irradiation •Trauma	**V. Drug–induced hypersecretion** •Dopamine receptor blockers •Atypical antipsychotics •Metoclopramide •Dopamine synthesis inhibitors– Methyldopa •Catecholamine depletors– Reserpine •Imipramines–Amitriptyline •Serotonin reuptake inhibitors– Fluoxetine • Estrogens and TRH
III. Pituitary hypersecretion •Prolactinoma •Acromegaly	**IV. Systemic disorders** •Chronic renal failure •Hypothyroidism and Cirrhosis •Pseudocyesis and Epileptic seizures

Prolactinoma

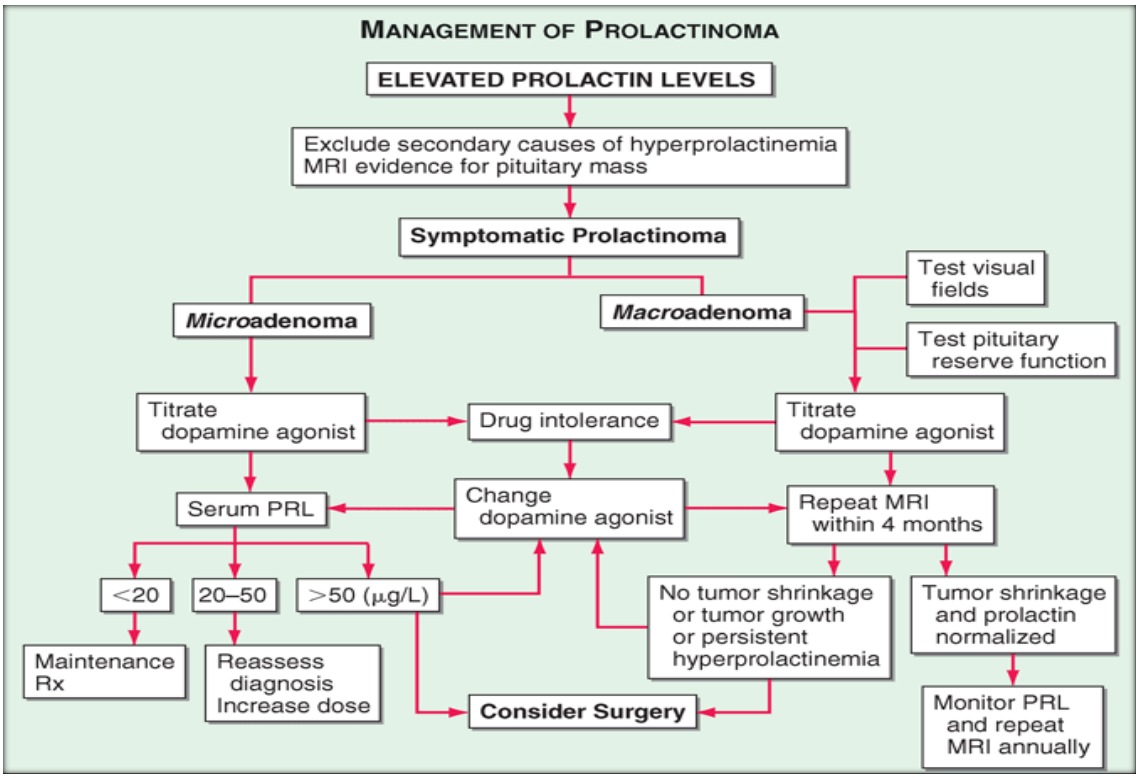
MC adenoma, MC Age - 20-30yrs



Lab Diagnosis-

- Measuring fasting morning prolactin level measured at frequent interval
- Pulsatile -

- **Prolactin level-**
  - PRL level >200 µg/L- Occurs only macroadenoma
  - PRL level 100-200 µg/L- strongly suggest macroadenoma
  - PRL levels <100µg/L - may be caused by microadenomas, other sellar lesions that decrease dopamine inhibition, or nonneoplastic causes of hyperprolactinemia.

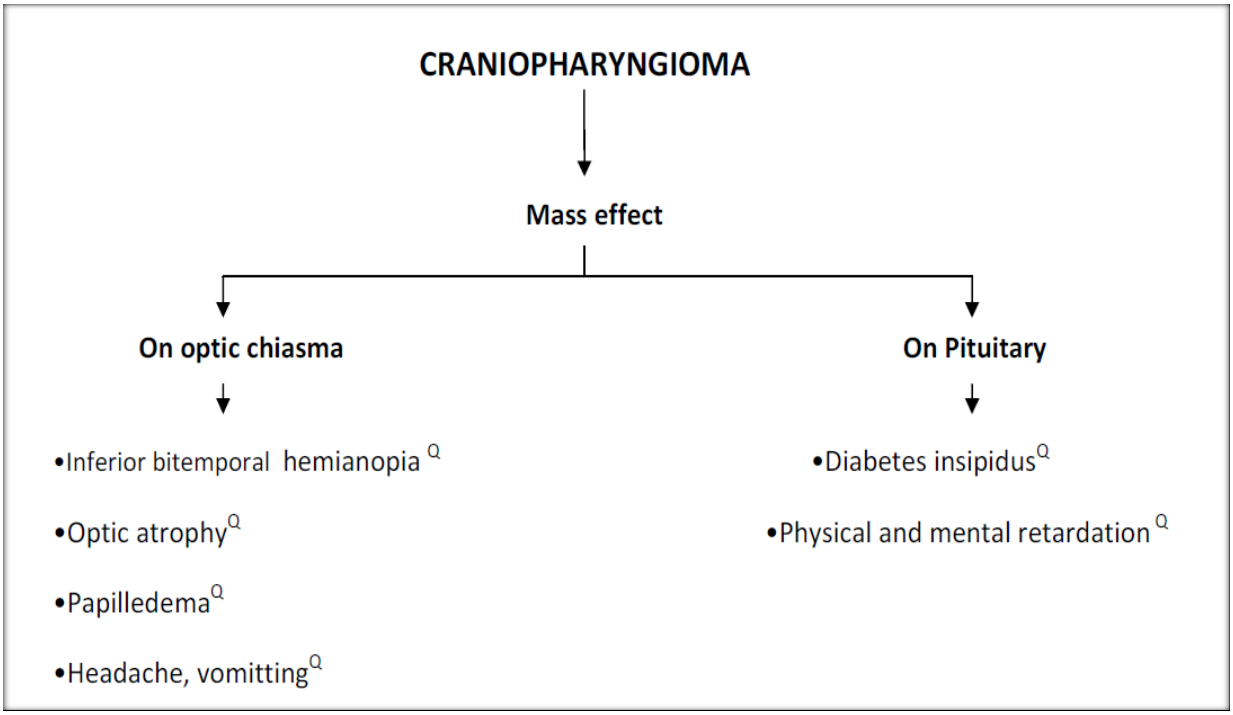


- **Medical- Oral dopamine agonists**
  - Cabergoline
  - Bromocriptine
- **Indication for surgery-**
  - Dopamine resistance / intolerance
  - Presence of invasive macroadenoma with compromised vision
  - Failure of medical t/t
- **Indication for radiotherapy-**

aggressive tumors that do not respond to maximally tolerated dopamine agonists and/or surgery

Prolactin normalization is seen in-

- 70% microadenoma following surgery
- 30% in macroadenoma following surgery



- Bimodal age incidence- child & 60yr
- Suprasellar location
- Never produces – any hormone
- No amenorrhoea or galactorrhea.

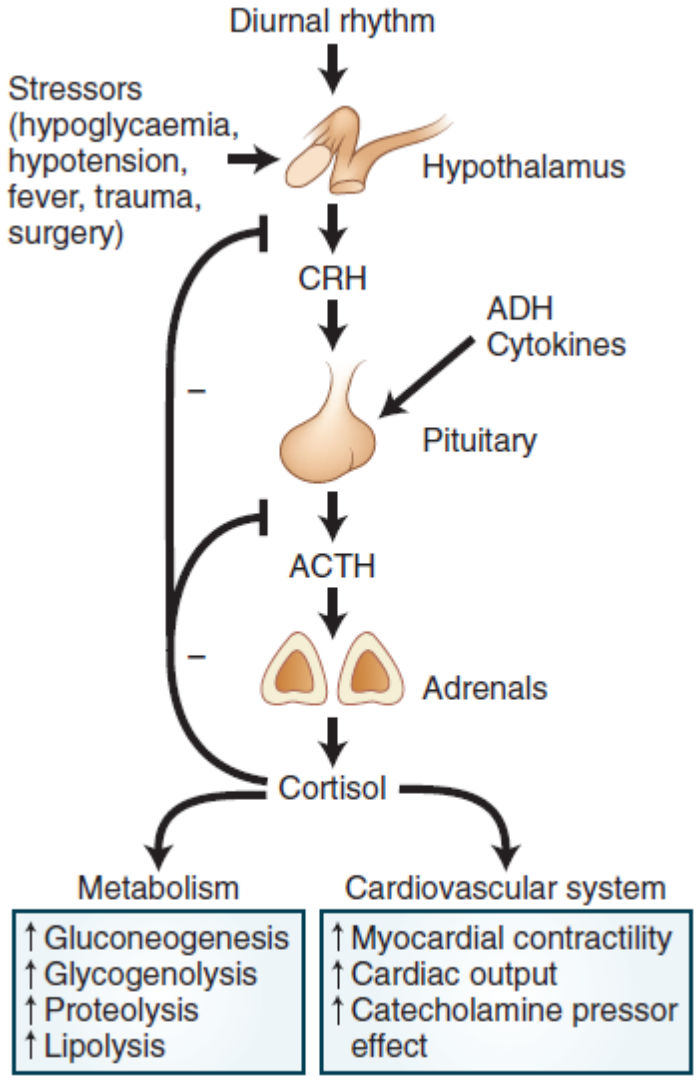
Treatment –

transcranial or transsphenoidal surgical resection followed by postoperative radiation of residual tumor

ACTH Producing Adenoma

- 70% of patients with endogenous causes of Cushing's syndrome.
- Account for about 10–15% of all pituitary tumors.
- Cushing's disease is 5–10 times more common in women than in men
- Exhibit unrestrained ACTH secretion, with resultant hypercortisolemia.
- However, they retain partial suppressibility in the presence of high doses of administered glucocorticoids,

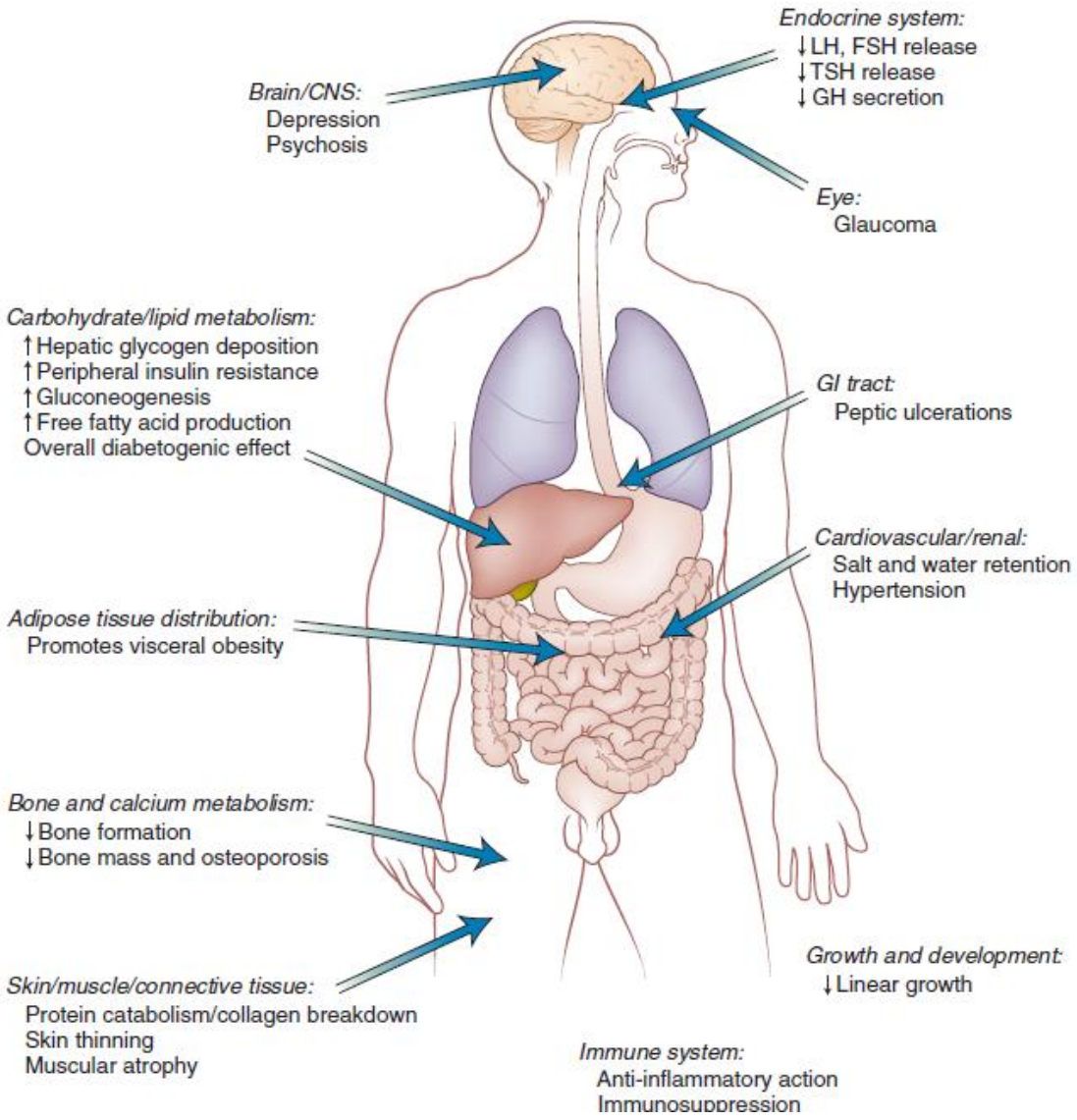
- providing the basis for dynamic testing to distinguish pituitary from nonpituitary causes of Cushing's syndrome.



A Regulation of cortisol secretion

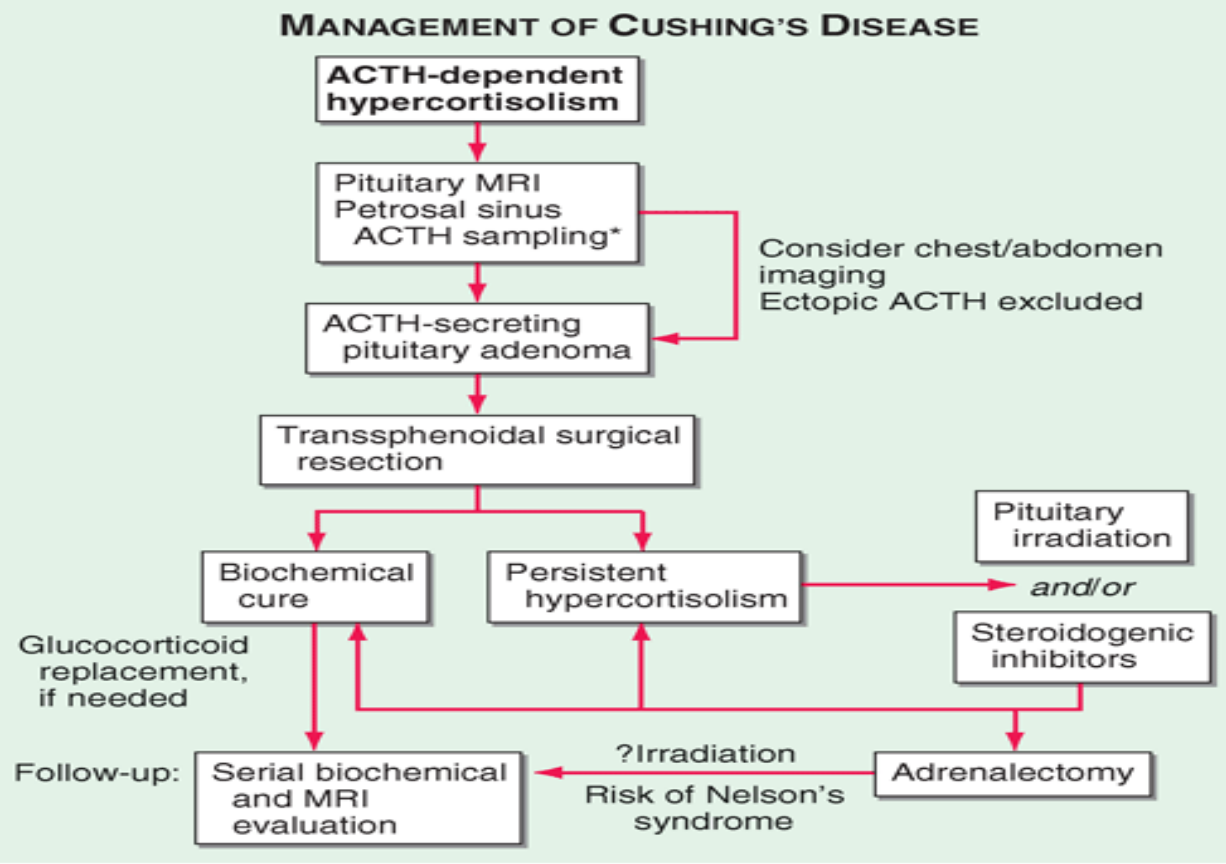
Hypothalamic-pituitary-adrenal axis

Adrenocorticotropic hormone (ACTH) is secreted from the anterior pituitary under the influence of two principal secretagogues, corticotropin-releasing hormone (CRH) and arginine vasopressin; other factors, including cytokines, also play a role. CRH secretion is regulated by an inbuilt circadian rhythm and by additional stressors operating through the hypothalamus. Secretion of CRH and ACTH is inhibited by cortisol, highlighting the importance of negative feedback control.



Body Part/System	**Signs and Symptoms**
Body fat	Weight gain, central obesity, rounded face, fat pad on back of neck ("buffalo hump")
Skin	Facial plethora, thin and brittle skin, easy bruising, broad and purple stretch marks, acne, hirsutism
Bone	Osteopenia, osteoporosis (vertebral fractures), decreased linear growth in children
Muscle	Weakness, proximal myopathy (prominent atrophy of gluteal and upper leg muscles)
Cardiovascular	Hypertension, hypokalemia, edema, atherosclerosis

Body Part/System	Signs and Symptoms
system	
Metabolism	Glucose intolerance/diabetes, dyslipidemia
Reproductive system	Decreased libido, in women amenorrhea (due to cortisol-mediated inhibition of gonadotropin release)
Central nervous system	Irritability, emotional lability, depression, sometimes cognitive defects, in severe cases, paranoid psychosis
Blood and immune system	Increased susceptibility to infections, increased white blood cell count, eosinopenia, hypercoagulation with increased risk of deep vein thrombosis and pulmonary embolism



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's*

Medical treatment- Ketoconazole,Metyrapone,Mitotane,Aminogluthemide,IV Etomidate

Nelson's syndrome

- most aggressive and rapidly growing of all pituitary tumours
- **Hyperpigmentation** (due to increased ACTH)
- **Symptoms** due to an expanding intrasellar mass lesion

  • Visual field defects • Headache

  • Cavernous sinus invasion • Extraocular muscle palsy

- Plasma ACTH levels are markedly elevated > 1000 pg/ml.

TESTS OF GLUCOCORTICOID RESERVE

Within minutes after administration of ACTH, cortisol levels increase in blood. This responsiveness can be used as an index of the functional reserve of the adrenal gland for production of cortisol. Patients with primary adrenal insufficiency have smaller responses.

A screening test (the so-called rapid ACTH stimulation test) involves the administration of 25 units (0.25 mg) of cosyntropin intravenously or intramuscularly and measurement of plasma cortisol levels before and 30 and 60 min after administration; the test can be performed at any time of the day. The most clear-cut criterion for a normal response is a stimulated cortisol level of >18 ug/dL, and the minimal stimulated normal increment of cortisol is >7 ug/dL above baseline.

Suggested Plan for Steroid Replacement in Patients Withdrawing from Chronic Corticosteroid Therapy

Pred Dose (mg/day)	DURATION OF GLUCOCORTICOID TREATMENT ≤3 wk*	>3 wk		
≥7.5	Can stop	↓ rapidly (e.g., 2.5 mg q3-4d) THEN		
5-7.5	Can stop	↓ 1 mg q2-4 wk THEN	OR	Convert 5 mg pred to 20 mg HC, then ↓ 2.5 mg/wk to 10 mg/day THEN
<5	Can stop	↓ 1 mg q2-4 wk		After 2-3 mo at HC 10 mg/day, administer SST/ITT: Pass → Withdraw Fail → Continue

*Beware of frequent steroid courses (e.g., in asthma).
HC, hydrocortisone; ITT, insulin tolerance test; pred, prednisolone; SST, short Synacthen test.

The commonest cause of Cushing's Syndrome in clinical practice is exogenous administration of glucocorticoids in supraphysiologic doses. Sudden stoppage of these large doses taken for prolonged duration is the commonest cause of secondary Adrenal insufficiency. Thus it is extremely important to understand the plan for gradual withdrawl of steroids and subsequent assessment of HPA axis if needed.

DISORDERS OF GROWTH HORMONE

- Secreted by somatotrophs (**50 %** of the anterior pituitary cells)
- *Pulsatile release* -**greater levels at night** (sleep)
- GH -necessary for **normal linear growth**.
- GH deficiency causes short stature;
- GH excess (prior to epiphyseal closure) leads to gigantism.
- **Controlled by** *a dual hypothalamic regulation*.
    - Secretion is stimulated by GHRH & Gherlin
    - Inhibited by somatostatin.
- GH rather **acts indirectly by** stimulating the formation *somatomedins or insulin-like growth factors* (IGFs)
- IGF-I (**somatomedin C**) - most important for postnatal growth.
- The liver is the main source of circulating IGF-I.
- GH is a **trophic factor for insulin release**, facilitating release in response to various secretagogues
- GH-deficient individuals have impaired insulin release to glucose challenge.
- GH act as an **insulin antagonist** to inhibit glucose uptake by tissues.
- Patients with GH deficiency are prone to insulin-induced hypoglycemia;
- *patients with GH excess develop insulin resistance*.
- **Hypoglycemia - P**otent stimulator for GH release

GROWTH HORMONE EXCESS: ACROMEGALY

- GH excess -
    - In children **before epiphyseal closure** produces gigantism
    - **After closure** produces acromegaly. -- insidious, chronic, debilitating disease associated with bony and soft tissue overgrowth.

- MC cause of excessive GH secretion is **pituitary adenoma**.
- *Up to one-fourth* of the adenomas secrete both GH and prolactin.
- Acromegaly may also be seen in-
    - **McCune-Albright syndrome** (consists of polyostotic fibrous dysplasia, a variety of endocrine disorders, including GH-secreting pituitary tumors, adrenal adenomas etc., and pigmented skin patches)
    - **Carney's complex** (atrial myxoma, spotty skin pigmentation, and acoustic neuroma).

Clinical features of Acromegaly

- Sex-Equally prevalent in men and women
- MC Age- **middle age.**
- **Soft tissue and bone enlargement**, which results-
- In increased hand, foot, and hat size, prognathism,
- enlargement of the tongue, wide spacing of the teeth
- Coarsening of facial features.
- **Increased heel pad thickness**, increased shoe or glove size, ring tightening.
- **Visceromegaly** -Cardiomegaly, macroglossia and thyroid ↑
- **Cartilage hypertrophy and osseous overgrowth** - lead to
- Degenerative arthritis, kyphoscoliosis, spinal stenosis.

- **CVS-** Coronary heart disease, cardiomyopathy with arrhythmias, left ventricular hypertrophy, decreased diastolic function, and hypertension occur in about 30% of patients.
- **Diabetes mellitus** - develops in one-third of the patients.
- Increased risk of colon polyps &**colonic malignancy**.
- Patients feel weak and tired.
- **Obstructive sleep apnea** leads to hypersomnolence.

- **Neurologic and musculoskeletal symptoms,**
    - Headaches, nerve entrapments and paresthesias (often due to carpal tunnel syndrome),
    - Muscle weakness, and arthralgias (particularly involving the shoulders, back, and knees).

Diagnosis

- Screening measure - **Serum IGF-1 levels** are elevated in acromegaly.
- Multiple measurement of GH- Due to pulsatility of GH secretion
- Confirmed diagnosis-

• By demonstrating the **failure of GH suppression** to <1µg/L within 1 to 2 h of an oral glucose load (75 g).

- **Prolactin** *should be measured* as it is elevated in up to one-fourth of patients with acromegaly.

Treatment-

- **Transsphenoidal surgical resection** --*preferred primary treatment* for both micro and macroadenomas.
- **Medical therapy—**
    - **Somatostatin analogues-Ex-** *Octreotide acetate, Sandostatin, Lanreotide*
    - **Pegvisomant,** a GH receptor antagonist
- **Indication–**

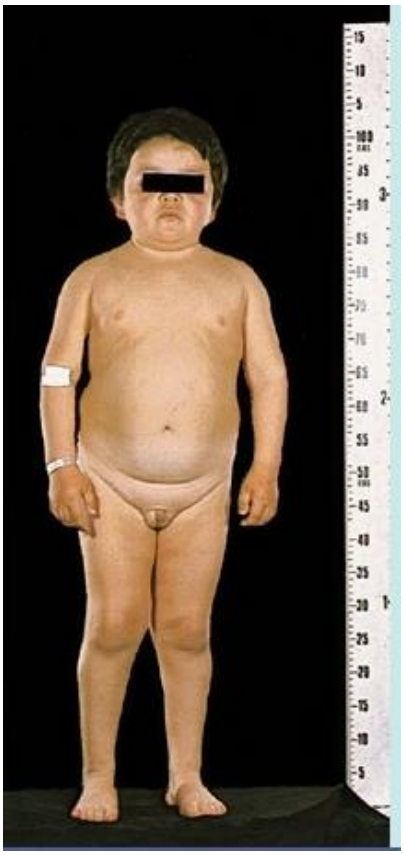
• *Adjuvant treatment* for preoperative shrinkage, • For large invasive macroadenomas,

• Immediate relief of symptoms • Reduction of GH hypersecretion

- **Bromocriptine or cabergoline--** if tumors secrete both PRL and GH.
- **Pituitary radiation** -who are not cured by surgical and medical therapy

GH Deficiency in children –

It is characterized by short stature, micropenis, increased fat, high-pitched voice and a propensity to hypoglycemia.Midline defects can be seen in patients with GHD In 1/3rd cases it is familial (Autosomal dominant, recessive or X-linked)



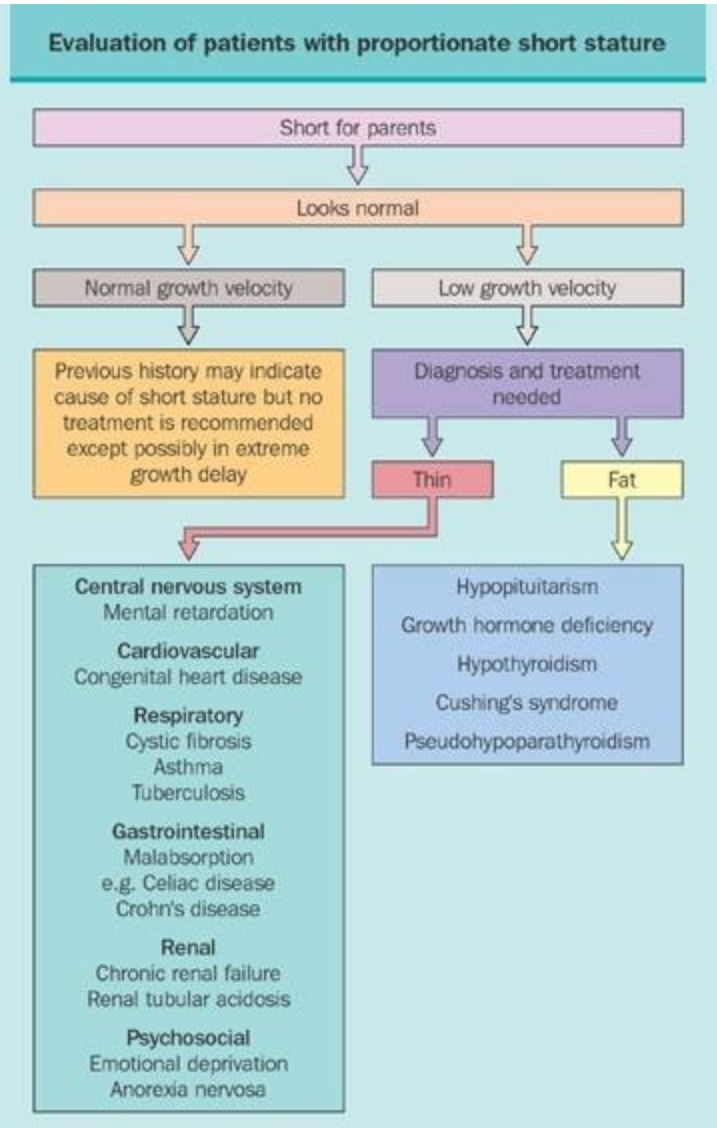
A boy with classic growth-hormone insufficiency.

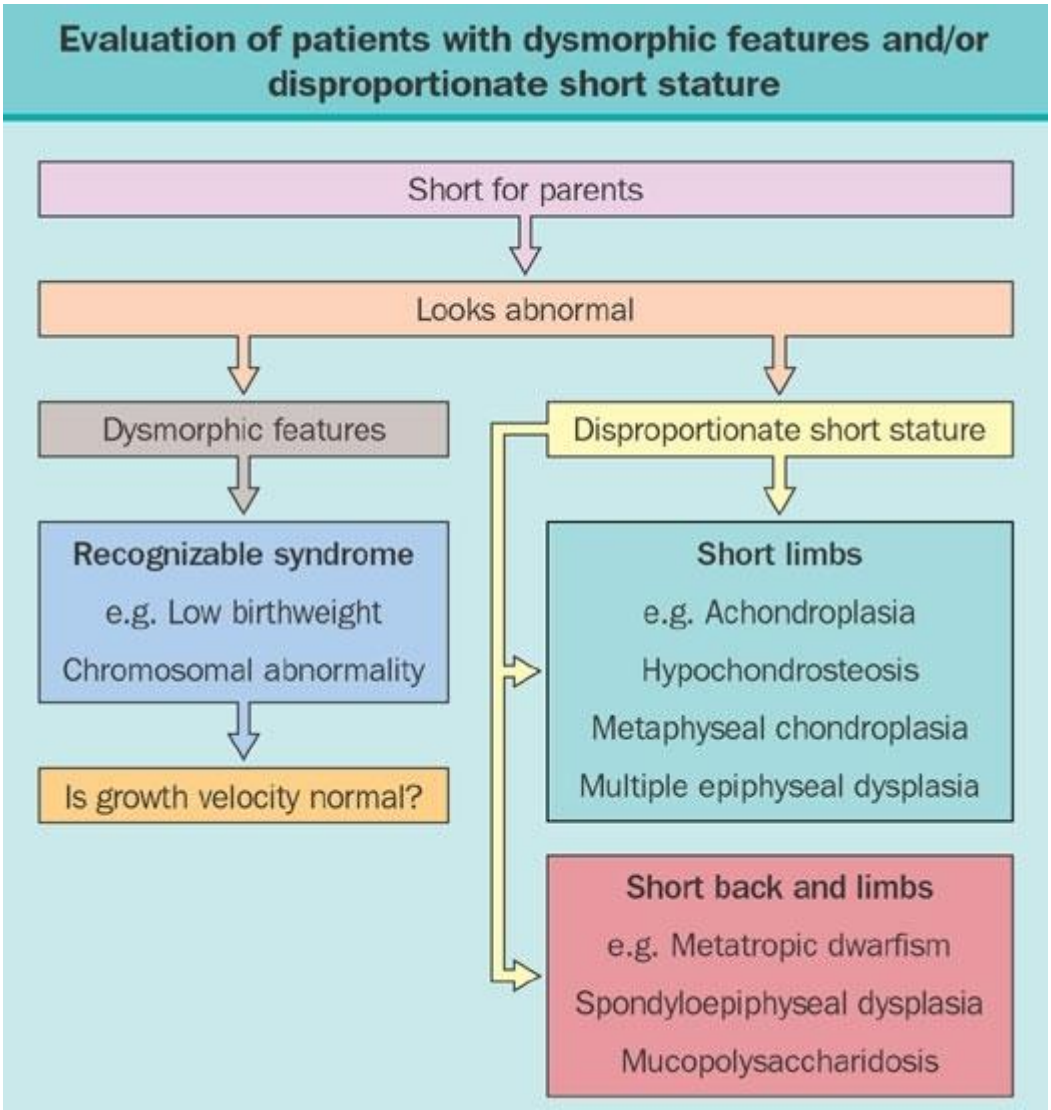
Such children are very small, tend to be obese, and have underdeveloped genitalia. They have a low growth velocity and usually a retarded bone age

- GHRH receptor mutations are associated with low basal GH levels that can not be stimulated by exogenous GHRH or insulin.
- GH insensitivity is caused by GH receptor defect or signaling defect. Laron syndrome is characterized by complete GH insensitivity evident by high GH levels, with decreased GHBP, and low IGF-I levels.

Short stature should be comprehensively evaluated if a patients' height is > 3SD below the mean for age or if growth rate has decelerated. Final height can be predicted by adding 6.5 cm (boys) or subtracting 6.5cm (girls) from the mid-parental height.

MED 5


Evaluation of patients with proportionate short stature
Short for parents
Looks normal
Normal growth velocity
Low growth velocity
Previous history may indicate cause of short stature but no treatment is recommended except possibly in extreme growth delay
Diagnosis and treatment needed
Thin
Fat
Central nervous system
Mental retardation
Cardiovascular
Congenital heart disease
Respiratory
Cystic fibrosis
Asthma
Tuberculosis
Gastrointestinal
Malabsorption
e.g. Celiac disease
Crohn's disease
Renal
Chronic renal failure
Renal tubular acidosis
Psychosocial
Emotional deprivation
Anorexia nervosa
Hypopituitarism
Growth hormone deficiency
Hypothyroidism
Cushing's syndrome
Pseudohypoparathyroidism



Diagnosis of GHD can be established by examining the response to provocative stimuli including exercise, insulin-induced hypoglycemia which normally increase GH to >10µg/L in children. Idealy atleast 2 stimulation tests should be done

Tests to Provoke Growth Hormone Secretion

Stimulus	Dosage	Times Samples Are Taken (min)	Comments
Sleep	Obtain sample from indwelling catheter	60-90 min after onset of sleep	
Exercise	Step climbing; exercise cycle for 10 minutes	0, 10, 20	Observe child closely when on the steps
Levodopa	<15 kg: 125 mg 10-30 kg: 250 mg >30 kg: 500 mg	0, 60, 90	Nausea, rarely emesis
Clonidine	0.15 mg/m^2	0, 30, 60, 90	Tiredness, postural hypotension
Arginine HCl (IV)	0.5 g/kg (max 30 g) 10% arginine HCl in 0.9% NaCl over 30 min	0, 15, 30, 45, 60	
Insulin (IV)*	0.05 to 0.1 unit/kg	0, 15, 30, 60, 75, 90, 120	Hypoglycemia, requires close supervision
Glucagon (IM)	0.03 mg/kg (max 1 mg)	0, 30, 60, 90, 120, 150, 180	Nausea, occasional emesis
GHRH (IV)†	1 µg/kg	0, 15, 30, 45, 60, 90, 120	Flushing, metallic taste

Treatment-

- Replacement therapy with recombinant GH 0.02 to 0.05mg/kg per day subcutaneously achieves growth velocity in GH-deficient children to ~10cm/year.
- GH treatment is also moderately effective for accelerating growth rate in children with Turner syndrome and chronic renal failure.
- In patients with GH insensitivity **(Laron syndrome)**, treatment with IGF-I bypasses the dysfunctional GH receptor.
- **IGF-I Physiology**
  IGF-I has been approved for use in patients with GH-resistance syndromes. Injected IGF-I (100µg/kg) induces hypoglycemia, and lower doses improve insulin sensitivity in patients with severe insulin resistance and diabetes. In cachectic subjects, IGF-I infusion (12µg/kg per hour) enhances nitrogen retention and lowers cholesterol levels. Longer-term subcutaneous IGF-I injections enhance protein synthesis and are anabolic. Although bone formation markers are induced, bone turnover also may be stimulated by IGF-I.

Adult GH deficiency-

Thisdisorder is usually caused by hypothalamic or pituitary somatotrope damage. The sequential order of hormone loss is usually GH→FSH/LH→TSH→ACTH.

Presentation – Body composition changes are common and include reduced lean body mass, increased fat mass with selective deposition of intra-abdominal visceral fat and increase waist to hip ratio. Hyperlipidemia, left ventricular dysfunction, hypertension and increase plasma fibrinogen level may also be present.

- Features of Adult Growth Hormone Deficiency
  Clinical
- Impaired quality of life
- Decreased energy and drive
- Poor concentration
- Low self-esteem
- Social isolation
- Body composition changes
- Increased body fat mass
- Central fat deposition
- Increased waist-hip ratio
- Decreased lean body mass

- Reduced exercise capacity
- Reduced maximum O_2 uptake
- Impaired cardiac function
- Reduced muscle mass
- Cardiovascular risk factors
- Impaired cardiac structure and function
- Abnormal lipid profile
- Decreased fibrinolytic activity
- Atherosclerosis
- Omental obesity

- **Imaging**
- Pituitary: mass or structural damage
- Bone: reduced bone mineral density
- Abdomen: excess omental adiposity
- **Laboratory**
- Evoked GH <3 ng/mL
- IGF-I and IGFBP3 low or normal
- Increased LDL cholesterol
- Concomitant gonadotropin,
- TSH, and/or ACTH reserve deficits may be present

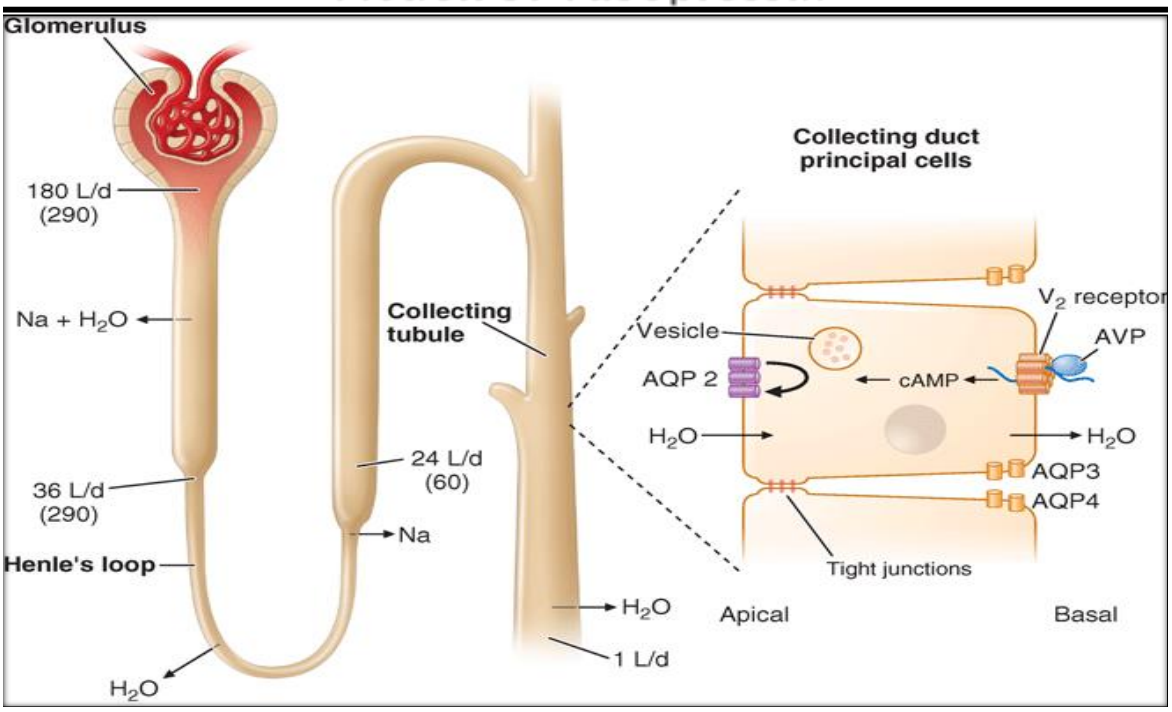
The most validated test is insulin- induced (0.05 to 0.1 u/kg iv) hypoglycemia. After glucose reduction to ~ 40 mg/dl, most individuals experience neuroglycopenic symptoms and peak GH release occurs at 60min and remains elevated for up to 2h. AGHD is defined by a peak GH response to hypoglycemia of < 3 μg\L. Insulin tolerance test is contraindicated in patients with diabetes, ischemic heart disease, cerebrovascular disease, epilepsy and in elderly patients. Treatment is replacement of GH. Contraindications to therapy include the presence of an active neoplasm, intracranial hypertension, uncontrolled diabetes and retinopathy.

Posterior Pituitary

Vasopressin (ADH) receptors

V1 Vasopressin receptors	V2 Vasopressin receptors
1. Blood vessels	**1. Blood vessels**
ADH constricts blood vessels through V1 receptors and can raise the B.P. but Much higher concentration is needed.	ADH acts on the collecting duct cells through V2 receptors . It increases the permeability of these cells for water. The water from the lumen diffuses into the interstitium.
2. Other smooth muscles	2.. **Vascular endothelium**
It causes contraction of visceral smooth muscles such as increased peristalsis in gut.	Causes release of von-willebrand's factor from vascular endothelium.
3. CNS -Causes ACTH release	**3.. Liver** -Causes release of coagulation factor VIII.
4. Liver-Increase hepatic glycogenolysis.	
5.Platelet-Cause platelet aggregation.	

Action of Vasopressin



Uses of ADH (Anti-diuretic hormone)-

1.Diabetes insipidus DI of pituitary origin is the most important indication for ADH or vasopressin

2. Bed wetting (Nocturia) in children

3. Bleeding esophageal varices

4. Haemophilia , von willebrand's disease

5. Renal concentration test

6. Before abdominal radiography

Normal values	
Serum Na	136–145 meq/l
Serum K	3.5–5.0 meq/l
Serum Osmolality	285–295 mmol/kg
Serum Urea	10–20 mg/dl
Urine Osmolality	350–1000 mosmol/kg

HYPONATREMIA

Defined as plasma sodium less than **135 mEq/L**.(incidence 1.5-2.5%)

Imp. Bcoz

- 1. Acute severe hyponatremia has substancially high morbidity and mortality.

- 2. Rapid correction of chronic hyponatremia can lead to neurological deficit and even death.
- 3. Etiology and treatment is not as simple as that of other electrolyte deficit.

Hyponatremia = sodium deficit so salt replacement is required in all is a wrong concept.

- **Hyponatremia usually means water retention**

Causes

i. Pseudohyponatremia

a. Normal osmolality - hyperlipidaemia, hyperproteinaemia

b. High osmolality - hyperglycaemia, mannitol

ii. Hypoosmolar hyponatremia (True hyponatremia)

a. Hyponatremia with ECF volume depletion

(patient dehydrated , reduction in total body Na exceeds reduction in total body water)

- **Extrarenal loss(urinary Na < 15 mEq/L)-** Vomiting,diarrhea,peritonitis.
- **Renal loss (urinary Na > 20 mEq/L)-**

Excessive diuretics, salt losing nephropathy,diabetic ketoacidosis, cerebral salt wasting syndrome.

b. **Hyponatremia with hypervolemia, increased ECF volume-** (patient oedematous – increase in total body water exceeds increase in total body Na)

- Urinary Na < 20 mEq/L : CHF, cirrhosis and nephritic syndrome.
- Urinary Na > 20 mEq/L : renal failure

c. **Hyponatremia with normal ECF volume**

(patient normovolemic, increased total body water)

- SIADH
- hypothyroidism
- post operative pain

- Glucocorticoid deficiency
- psychogenic polydypsia,
- Nausea

Clinical features of hyponatremia

Mild	Moderate	Severe
Anorexia	Personality changes	Drowsiness
Headache	Muscle cramps	Diminished reflexes
Nausea	Muscular weakness	Convulsions
Vomotting	Confusion	Coma
Lethargy	Ataxia	Death

Major steps in initial evaluation of hyponatremia

1.Plasma osmolality

- Low : true hyponatremia
- Normal or elevated : pseudohyponatremia or renal failure

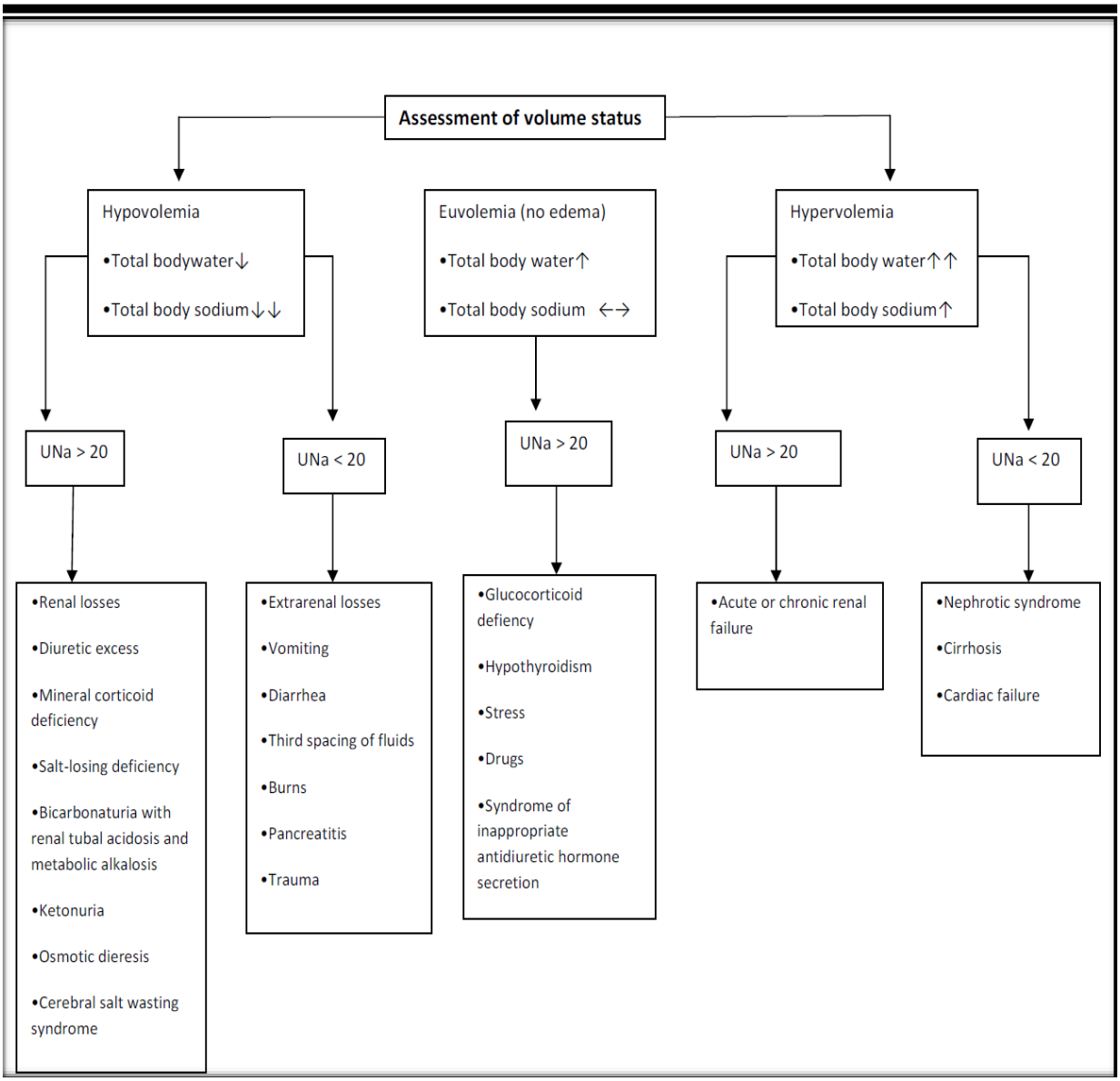
2.urine osmolality

- < 100 mOsm/kg or specific gravity < 1.003, diluted urine suggest primary polydipsia with normal water excretion
- >100mosm/kg , other causes of hyponatremia in which water excretion is impaired.

3.urine Na conc. :

- <15 mEq/L effective volume depletion e.g diarrhea, vomiting
- >20 mEq/L SIADH (normo volemia) or renal salt wasting (diuretics, renal diseases or hypoaldosteronism)
- **Associated hyperkalemia** suggests renal insuffiency or adrenal insuffiency with hypoaldosteronism.
- **Associated hypokalemiaand metabolic alkalosis** suggest vomiting or diuretic therapy.
- Diuretics induced hyponatremia is almost always **due to** thiazide diuretics (loop diuretics :water dieresis >natriuresis , so hyponatremia infrequent .

Approach to hyponatremia



Treatment

Goal of therapy

1. To raise the plasma Na conc. At a safe rate.
2. To replace Na deficit or K deficit or both.
3. To correct underlying etiology.

Choosing the appropriate therapy in hyponatremia

- **The choice of therapy varies with-**

• Acute (<48hrs)or chronic(>48hrs) • Severity of hyponatremia • Presence or absence of symptoms

A) Severe hyponatremia with seizures/other severe neurological abnormalities/with symptomatic hyponatremia

- **100ml bolus of 3% saline-**
  - Should not be corrected rapidly, as it causes **Central pontine demylination.**
  - **I**nitial rise should be 1.5-2mEQ/LT/hr for first 3-4 hrs,rise in sodium conc.should not exceed 10-12 mEQ in first 24 hrs.
  - Stopped once sodium-120-125 meq/l or symp.disappears..

b.Mild to moderate symptoms

- Require initial administration of hypertonic saline therapy.
- The serum Na should be raised at - 1meqLL/hour for 3-4 hrs.
- Then- fluid restriction and oral salt tablets.

c.Asymptomatic hyponatremia

- These patients have serum Na b/w 120-129 meq/L.
- Only with fluid restriction- may be sufficient
- Vaptans • Salts • Loop diuretic

Action of ADH or vasopressin –

- Act on the collecting tubuleof the kidney.
  - Collecting tubule becomes permeable to water
  - Thus allowing water to move out in the medullary interstitium from the tubules.

- Normally ADH is secreted –
  - In response to the increasing osmolality of the plasma
  - Leads to – stimulation of hypothalamic osmoreceptors
  - Which cause secretion of ADH from the posterior pituitary

Causes of Syndrome of Inappropriate Antidiuresis (SIADH)	
Neoplasms	
Carcinomas–	Lung, Duodenum, Pancreas, Ovary, Bladder, Ureter
Other –	Thymoma, Mesothelioma, Bronchial adenoma
Head trauma	Closed and penetrating
Infections–	Pneumonia, TB, meningitis, encephalitis, abscess, cavitation and AIDS
Vascular–	CVA, Cavernous sinus thrombosis
Genetic–	X–linked recessive (V_2 receptor gene)
Neurologic–	Multiple sclerosis, ALS, GBS, peripheral neuropathy
Congenital–	Corpus callosum agenesis, cleft lip/palate
Metabolic–	Acute intermittent porphyria, Asthma, Pneumothorax
Drugs–	Vasopressin , Chlorpropamide, Vincristine, Cyclophosphamide, Carbamazepine, antidepressant and antipsychotics

SIADH

- Syndrome of Inappropriately increased secretion of ADH from the posterior pituitary

(***irrespective of the osmolarity of the plasma***)

- This excess secretion of ADH leads to
  - Excessive water conservation.
  - Excessive urinary concentration resulting in passing of small amount of concentrated urine.
  - Excessive water retention in turn produces severe hyponatremia.
- Due to the retention of water-

- Certain compensatory mechanisms occurs,
- which leads to natriuresis.

- The natriuresis compensates for the slight increase in volume from ADH secretion and it also leads to increase in urinary sodium concentration.
- Mechanisms that regulate sodium excretion in response to increase in extracellular volume are -
  - Suppression of rennin angiotensin axis
  - Suppression of sympathetic system
  - Increased secretion of atrial natriuretic factor
- Compensatory mechanisms account for-
  - Increase in urinary sodium
  - Do not allow the extracellular volume to increase in amounts to produce clinical hypervolemia, hypertension or edema
  - Responsible for the unique finding of **hyponatremia with increase in urinary sodium.**
- Clinical feature of SIADH-
  - Hyponatremia (Na <135 mEq/l)
  - ↑ urine osmolality inappropriately (>150 mosm/kg)
  - ↑ urine Na excretion (μ Na >30 mEq/l)
  - ↓ Serum osmolality (<280 mosm/kg)
- This finding occurs-
  - Absence of diuretic therapy
  - Presence of euvolumia without edema
  - Absence of hypo/hyperkalemia and acidosis/alkalosis.
  - In setting of normal CVS/renal/adrenal/thyroid/hepatic function

Water loading test in SIADH

- Water loading or ADH testing -performed in hyponatremia pts
- Specific quantities of water is given to the patient and
- **Amount of urine produced and the changes in urine osmolarity and blood osmolarity are monitored.**
- A normal person should excrete **> 90%** of the water load in 4 hr
- Patients with SIADH - excrete **20-30 %** of the water load.
- The urine osmolality is high relative to plasma osmolality-suggest that pt. not excrete adequate water.

TREATMENT OF SIADH

Treat underlying etiology

- **Acute** : water restriction ,avoid hypotonic fluids,
    - hypertonic saline/oral NaCl
    - frusemide
- **chronic** : water restriction

high salt , high protein diet, frusemide, demeclocycline, lithium,vaptans,fludrocortisone.

- Aim for a gradual rise of Na to 125mEq/L at a safe rate.
- **Fluid restriction-** suggested goal intake of less than 800ml/day.
- Administration of NaCl- **hypertonic saline**
    - The osmolality of the **administered fluid must be greater than the osmolality of urine**
- **Loop diuretic – Needed if** urine osmolality is more than twice the plasma osmolality
- **Vasopressor receptor antagonist(vaptans)**
    - Increases free water excretion without loss of Na or K.
    - Ex--Intravenous conivaptan, oral tolvaptan .

- **In chronic SIADH,** the hyponatremia can also be corrected by treatment with **demeclocycline,** or **fludrocortisone**

HYPERNATREMIA

- ***Defined as plasma Na conc. > 145 mEq/L.***

ETIOLOGY OF HYPERNATREMIA

1. Excess water loss

a. insensible loss:

•dermal : heat exposure ,severe burns, severe exercise • Respiratory: patient on mechanical ventilator.

b. renal loss:

• diabetes insipidus (central or nephrogenic) • excessive diuretics, uncontrolled DM

c . gastrointestinal losses:

osmotic diarrhea.

2.Water deficit due to impaired thirst.

Primary hypodypsia, confused or comatose conditions.

3.Na retention

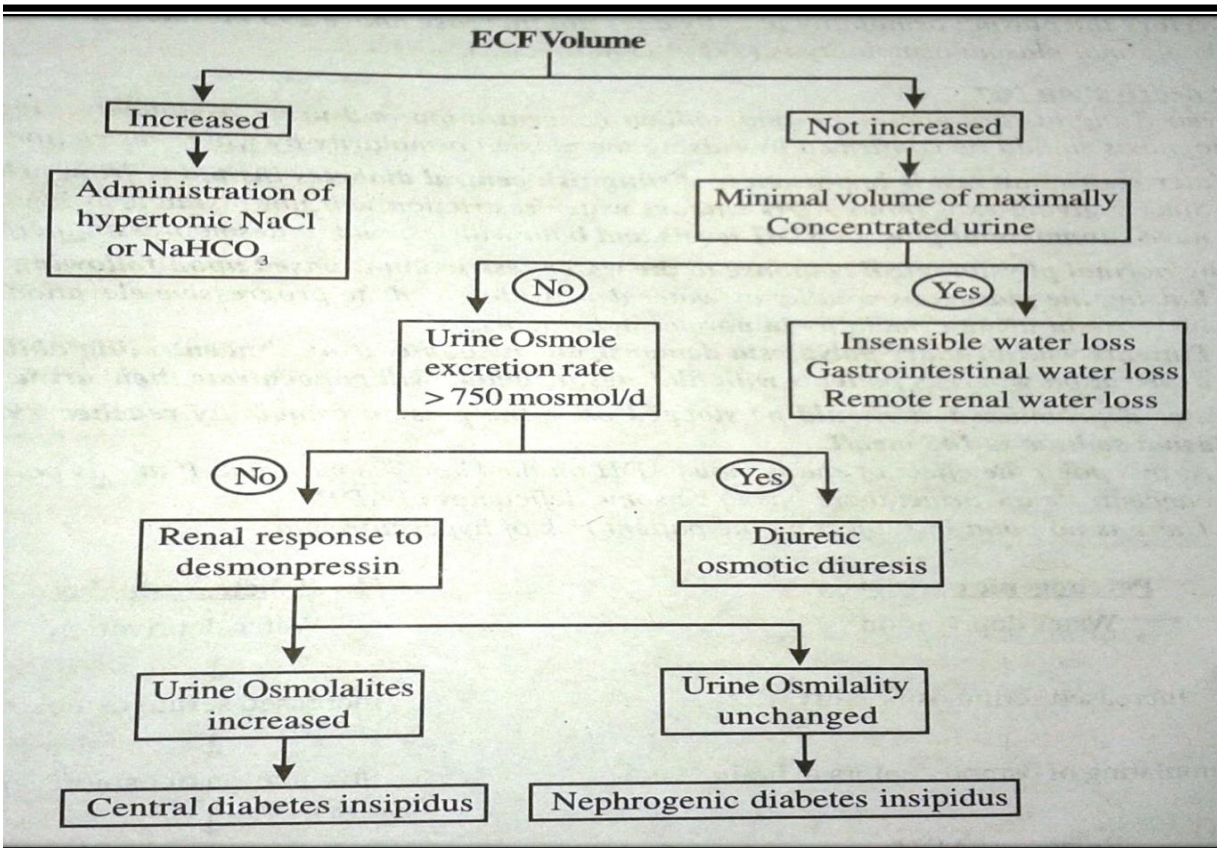
Excessive I.V. hypertonic NaCl or NaHCO3

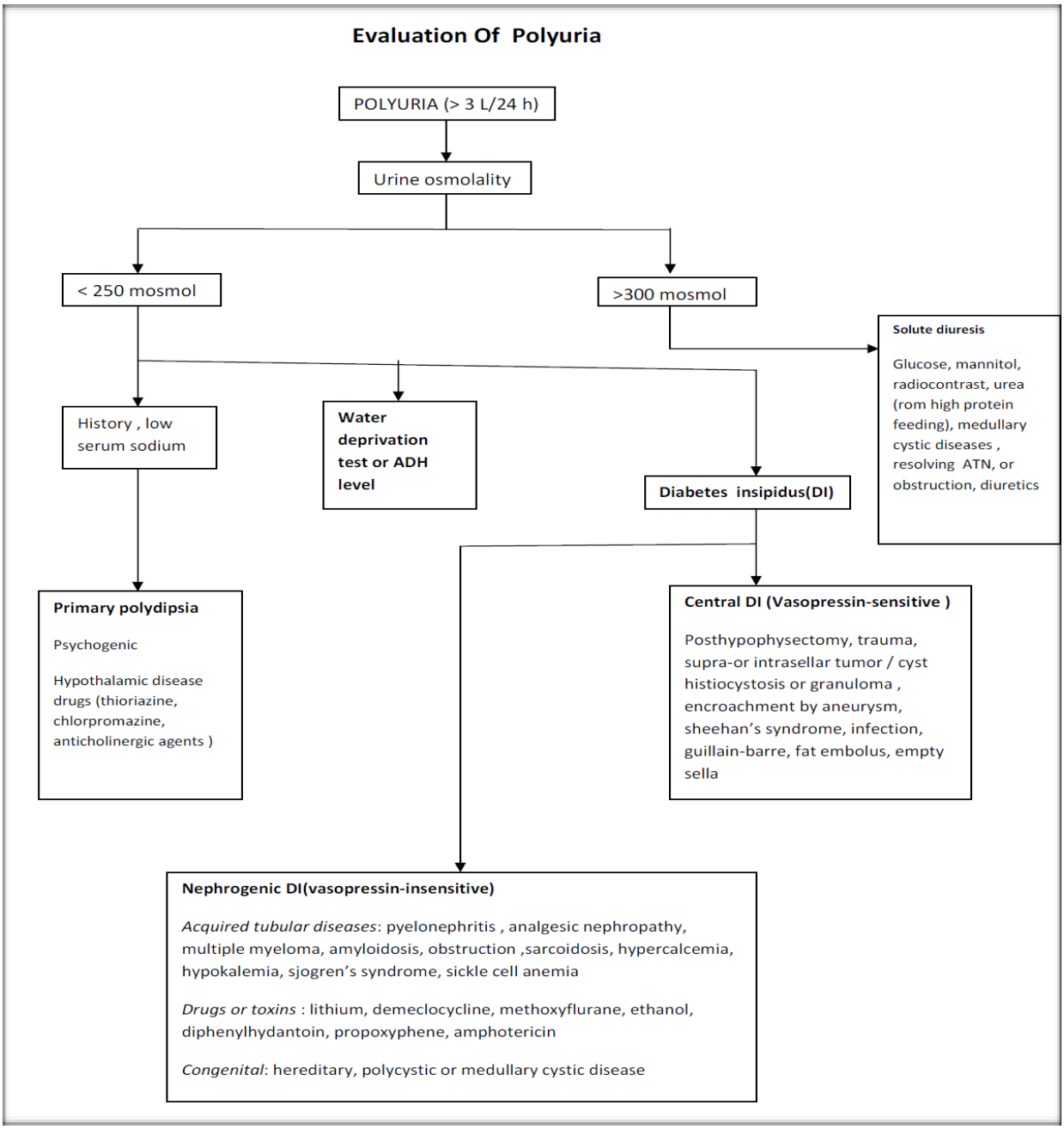
CLINICAL FEATURES

- Clinical features of hypernatremia are primarily neurological and they depend upon the rapidity of onset, its duration & magnitude.
- This is the state in which **dry sticky mucous membrane is characteristic & body temp. is generally elevated**.
- Major neurological symptoms- nausea, muscular weakness,altered mental status, neuromuscular irritability, focal neurological deficit, occasionally coma or seizures.
- In severe acute hypernatremia-

- brain shrinkage may be substantial, exerting traction on the venous sinuses.
- intracerebral & subarachnoid haemorrhage producing irreversible neurological deficit or even death.
- polyuria or excessive thirst.
- vol. depletion with history of excessive sweating, diarrhea or osmotic diuresis.

Clinical approach to hypernatremia





Treatment

- To stop ongoing fluid loss by treating the underlying causes
- To correct water deficit.

In acute hypernatremia the water deficit can be replaced relatively rapid, without increasing the risk of cerebral oedema.

Acute hypernatremia- targeted rate of correction is **1mEq/L/hr**.

Chronic hypernatremia - Rapid correction is dangerous.

- It may lead to neurological problems due to development of cerebral oedema.
- Safe rate of correction is reduction of serum Na by **1mEq/every 2 hrs or 10 mEq/L over first 24 hrs.**
- The safest route of administration of water is by mouth or via a nasogastric tube.

Hypernatremia with ECF volume contraction :

- if there is severe loss of ECF volume with hypotension and azotemia , isotonoic saline is given initially until the ECF volume is restored.
- Subsequently water deficit can be replaced with water by mouth or I.V. 5%-dextrose or 0.45% NaCl.

Hypernatremia with increased ECF volume:

- In these patients hypernatremia is secondary to solute administration.
- These patients are usually vol. overloaded.
- A loop diuretic is administered along with water to facilitate Na excretion.
- In patient with massive overload or renal failure dialysis may be necessary.

Diabetes insipidus

Diabetes insipidus

Pituitary diabetes insipidus	
Genetic	AD,AR(*AVP-neurophysin gene*) , X-linked
Congenital –	Midline craniofacial defects, Hypogenesis
Head trauma	
Neoplasms	Primary and Metastatic
Granulomas	Sarcoidosis, Histiocytosis
Infectious	Chronic meningitis, Viral encephalitis,
Inflammatory	Lymphocytic infundibulo neurohypophysitis, Granulomatosis with polyangiitis (Wegener's), SLE
Chemical toxins	Snake venom
Vascular	Sheehan's syndrome, Aneurysm
Pregnancy	Vasopressinase

Nephrogenic diabetes insipidus	
Genetic	X-linked recessive (*AVP receptor-2 gene*) , AD/AR(AQP2 gene)
Drugs	Li, Demeclocycline, Methoxyflurane,AMP-B, Aminoglycosides, Cisplatin
Metabolic	Hypercalcemia, hypercalciuria, Hypokalemia
Obstruction	(ureter or urethra)
Vascular	ATN, Sickle cell disease
Granuloma	Sarcoidosis
Neoplasm	Sarcoma
Infiltration	Amyloidosis
Pregnancy	

Primary Polydipsia	
1.Psychogenic	Schizophrenia,OCD
2.Dipsogenic	Abnormal thirst
Granuloma	Sarcoidosis
Infection	Tuberculous meningitis
Head trauma	Closed and penetrating
Demyelination	Multiple sclerosis
Drugs	Li, Carbamazepine
3.Iatrogenic	

Clinical feature

- urinary frequency
- Nocturia enuresis
- persistent thirst.Volume of urine>50 ml/kg
- Urine osmolarity<300mosm/L
- Plasma osmolarity ≥295mosm/L

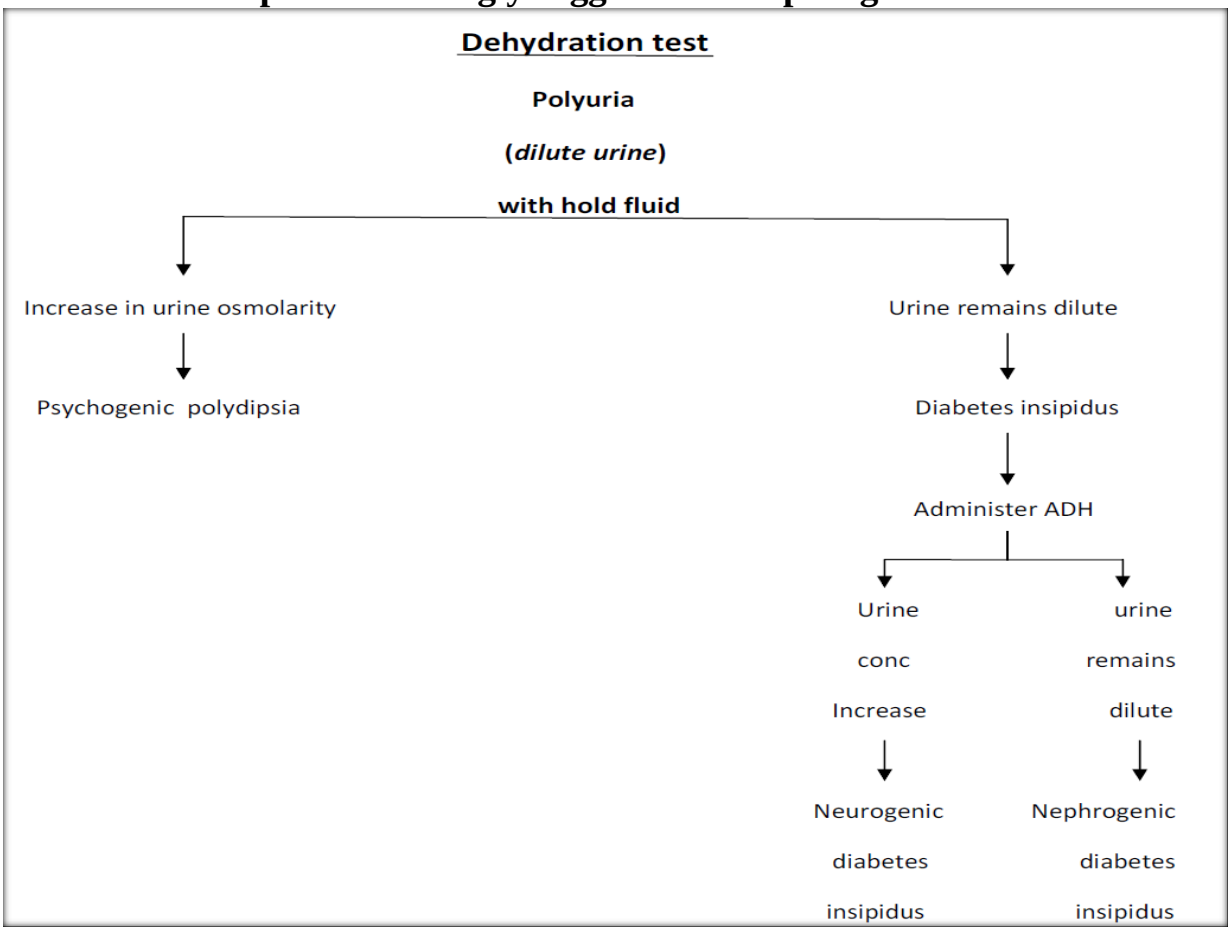
DIAGNOSIS

WATER DEPRIVATION TEST-

If **fluid deprivation** does not result in urine concentration **(osmolarity >300 mosmol/L, specific gravity >1.010)**

before

- body weight decreases by 5% or
- plasma osmolarity or sodium rise above the upper limit of normal,
- then patient has **severe pituitary or severe nephrogenic DI.**
- Distinguished by **administering desmopressin (0.03 g/kg SC or IV) and repeating the measurement of urine osmolarity 1–2 hours later**.
- **An increase of >50% indicates severe pituitary DI, whereas a smaller or absent response is strongly suggestive of nephrogenic DI**.



Other tests-

1.Plasma AVP Conc.

2.MRI

In most healthy adults and children, the posterior pituitary emits a hyperintense signal in T1-weighted midsagittal images.

This "**bright spot**" is almost always present in patients with primary polydipsia but is invariably absent or abnormally small in patients with pituitary DI.

It is usually also small or absent in nephrogenic DI presumably because of high secretion and turnover of AVP.

Thus, a normal bright spot

- virtually excludes pituitary DI,--
- argues against nephrogenic DI, and
- strongly suggests primary polydipsia.

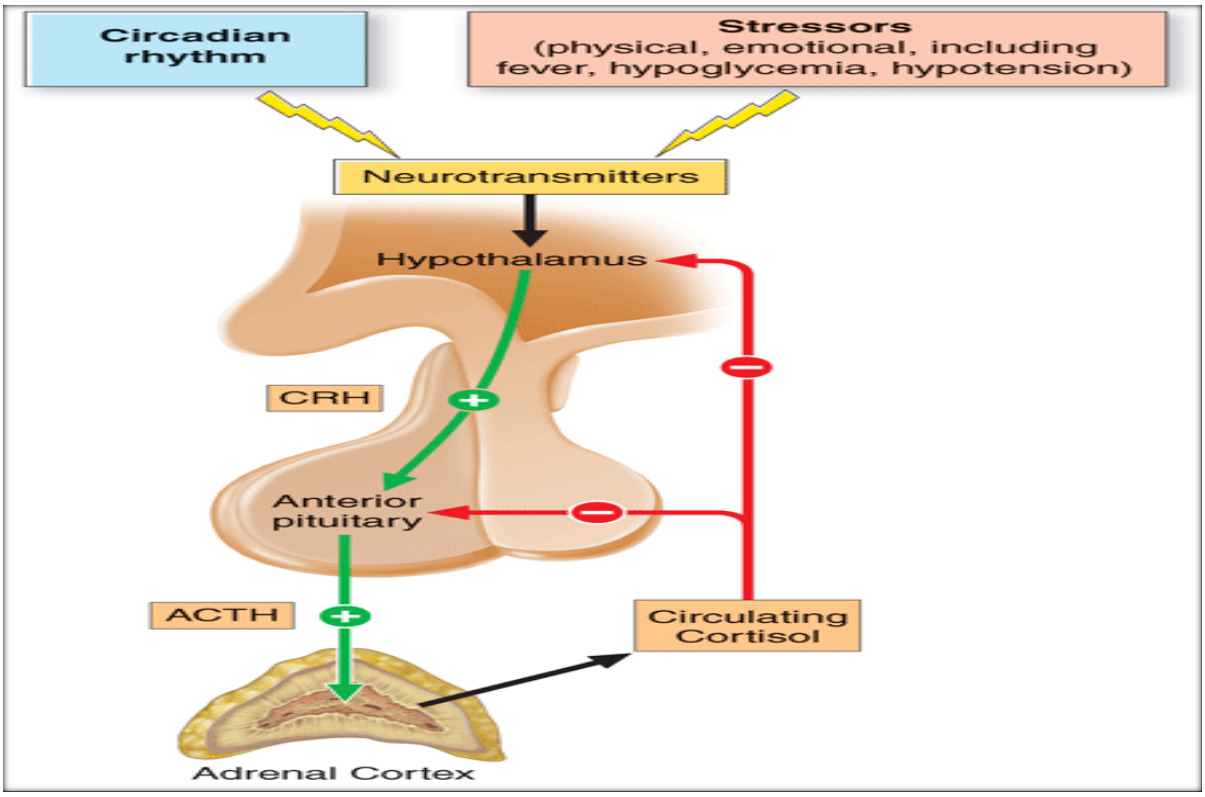
Lack of the bright spot is less helpful, because it is absent also in some healthy adults and patients with empty sella who do not have DI or AVP deficiency.

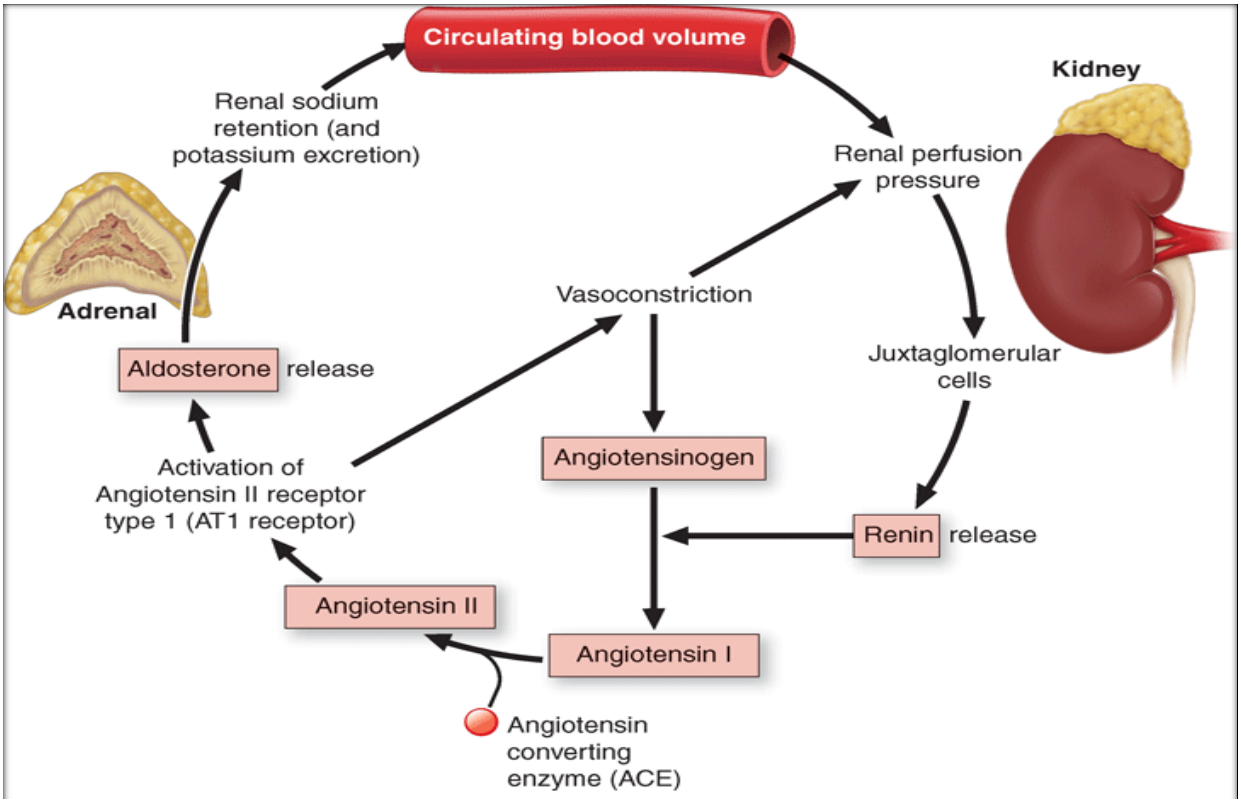
Treatment

- Treatment for pituitary DI-
    - Desmopressin (DDAVP)-
        - selectively at V_2 receptors agonist
        - given by IV or SC injection, nasal inhalation, or oral
    - Chloropromide
    - Carbamazepine
- Treatment for Nephrogenic DI-
    - Thiazide diuretics
    - NSAIDS

Adrenal Gland

MED 5


Circadian rhythm
Stressors (physical, emotional, including fever, hypoglycemia, hypotension)
Neurotransmitters
Hypothalamus
CRH
Anterior pituitary
ACTH
Circulating Cortisol
Adrenal Cortex


Circulating blood volume
Kidney
Renal sodium retention (and potassium excretion)
Renal perfusion pressure
Adrenal
Vasoconstriction
Aldosterone release
Juxtaglomerular cells
Angiotensinogen
Activation of Angiotensin II receptor type 1 (AT1 receptor)
Renin release
Angiotensin II
Angiotensin I
Angiotensin converting enzyme (ACE)

MC cause is iatrogenic steroid therapy

Causes of Cushing's Syndrome	%
ACTH-Dependent Cushing's	**90 %**
Cushing's disease (= ACTH-producing pituitary adenoma)	75%
Ectopic ACTH syndrome (due to ACTH secretion by bronchial or pancreatic carcinoid tumors, small cell lung cancer, medullary thyroid carcinoma, pheochromocytoma and others)	15%
ACTH-Independent Cushing's	10%
Adrenocortical adenoma	5-10%
Adrenocortical carcinoma	1%
Rare causes- ACTH-independent massive adrenal hyperplasia; McCune-Albright syndrome,etc	<1%

Syndromes associated with cushing-

- ***McCune-Albright syndrome***- also associated with polyostotic fibrous dysplasia, unilateral café-au-lait spots, and precocious puberty.
- ***Carney's complex-*** associated with cardiac myxomas, hyperlentiginosis, Sertoli's cell tumors, and PPNAD(primary pigmented nodular adrenal disease)

Cushing syndrome: Clinical features

Effect of glucocorticoids	Symptoms produced
On protein metabolism •Increased mobilization of protein from the tissues except the liver .	•Loss of proteins from the muscle causes severe weakness usually in proximal muscles. • large **purplish striae in skin** where they have torn apart .
On glucose metabolism •Stimulation of gluconeogenesis •Decreased glucose utilization by the cells	•Elevated blood glucose concentration and**"adrenal diabetes".**
On Na^+ and water homeostasis •Large Glucocorticoids may exert a **significant mineralocorticoid** action	•Salt and water retention leads to hypertension. **(Hypernatremia), Edema** •Significant K^+ depletion **(Hypokalemia)**
Blood and immune system	Increased susceptibility to infections, increased white blood cell count, eosinopenia, hypercoagulation with increased risk of deep vein thrombosis and pulmonary embolism

Effect of Glucocorticoids	Symptoms produced
On bone metabolism **Excess bone metabolism** causes- • ↓ in bone formation • ↑ in bone resorption	**Osteoporosis**
On fat metabolism Characteristic deposition of fat- Most probably due to- • insulin resistance or • elevated insulin levels.	•**Buffalo torso :** Due to Mobilization of fat from the lower part of the body with concomitant extra deposition of fat in the thoracic and upper abdominal regions •Edema of the face (**moonfacies"**)
On sex hormones adrenal androgens ↑ secretion Suppression of gonadotropins	•Hirsuitism •Acne •Oligomenorrhoea •Amenorrhoea
On C.N.S Excess glucocorticoid accelerates the basic electroencephalographic rhythm	•Increase appetite •Insomnia •Euphoria •Frank psychosis(acute paranoid)

Diagnosis of Cushing syndrome

Diagnostic flowchart for evaluating patients suspected of having Cushing's syndrome

Signs and symptoms of

Cushing's syndrome

↓

Screening test for cushing's syndrome

*Measurement of cortisol production after the administration of **1 mg***

***dexamethasone** at midnight*

↓

No suppression of cortisone

↓

Now, the definitive diagnosis of Cushing's syndrome

Cortisol response after the administration of 0.5mg

Dexamethasone every 6 hourly for 2 days

(Low dose dexamethasone test)

↓

No suppression on low dose dexamethasone

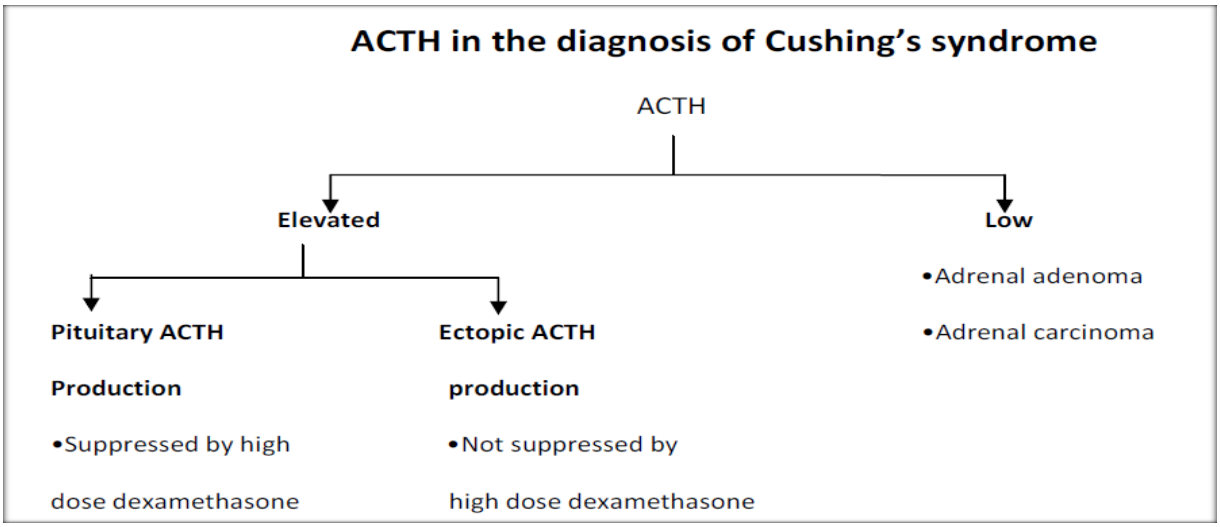
↓

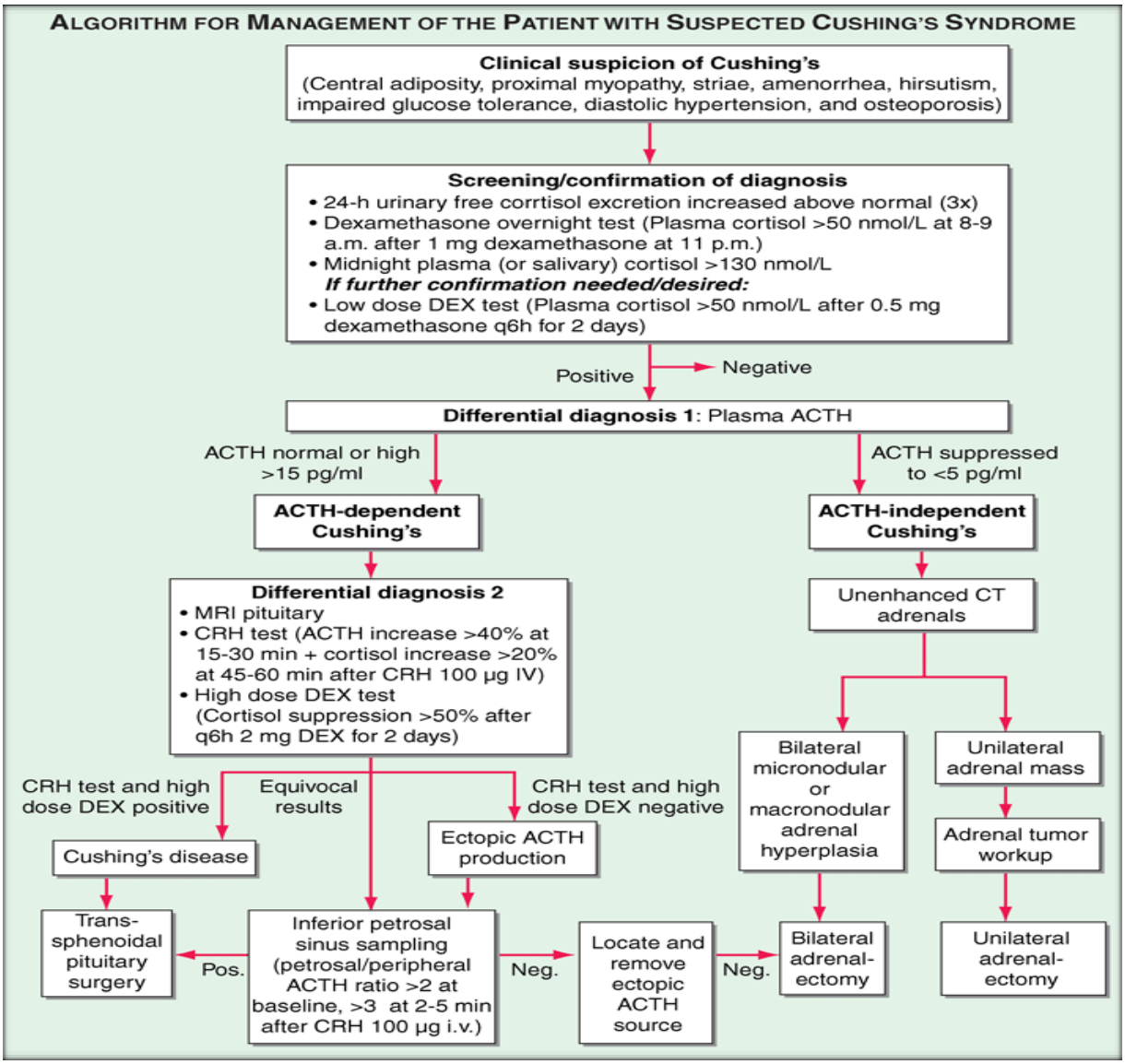
Diagnosis of cushing's syndrome is confirmed

↓

n normal person	Low dose dexamethasone suppresses cortisol secretion.
n Cushing's syndrome	Low dose dexamethasone is unable to suppress cortisol secretion
When Cushing's syndrome Is caused due to ectopic ACTH production	Even high dose dexamethasone is unable to suppress cortisol secretion.

MED 5


ACTH in the diagnosis of Cushing's syndrome
ACTH
Elevated
Low
•Adrenal adenoma
•Adrenal carcinoma
Pituitary ACTH
Production
•Suppressed by high
dose dexamethasone
Ectopic ACTH
production
•Not suppressed by
high dose dexamethasone


ALGORITHM FOR MANAGEMENT OF THE PATIENT WITH SUSPECTED CUSHING'S SYNDROME
Clinical suspicion of Cushing's
(Central adiposity, proximal myopathy, striae, amenorrhea, hirsutism, impaired glucose tolerance, diastolic hypertension, and osteoporosis)
Screening/confirmation of diagnosis
• 24-h urinary free corrtisol excretion increased above normal (3x)
• Dexamethasone overnight test (Plasma cortisol >50 nmol/L at 8-9 a.m. after 1 mg dexamethasone at 11 p.m.)
• Midnight plasma (or salivary) cortisol >130 nmol/L
If further confirmation needed/desired:
• Low dose DEX test (Plasma cortisol >50 nmol/L after 0.5 mg dexamethasone q6h for 2 days)
Positive
Negative
Differential diagnosis 1: Plasma ACTH
ACTH normal or high >15 pg/ml
ACTH suppressed to <5 pg/ml
ACTH-dependent Cushing's
ACTH-independent Cushing's
Differential diagnosis 2
• MRI pituitary
• CRH test (ACTH increase >40% at 15-30 min + cortisol increase >20% at 45-60 min after CRH 100 µg IV)
• High dose DEX test (Cortisol suppression >50% after q6h 2 mg DEX for 2 days)
Unenhanced CT adrenals
CRH test and high dose DEX positive
Equivocal results
CRH test and high dose DEX negative
Bilateral micronodular or macronodular adrenal hyperplasia
Unilateral adrenal mass
Cushing's disease
Ectopic ACTH production
Adrenal tumor workup
Trans-sphenoidal pituitary surgery
Pos.
Inferior petrosal sinus sampling (petrosal/peripheral ACTH ratio >2 at baseline, >3 at 2-5 min after CRH 100 µg i.v.)
Neg.
Locate and remove ectopic ACTH source
Neg.
Bilateral adrenal-ectomy
Unilateral adrenal-ectomy

Medical management

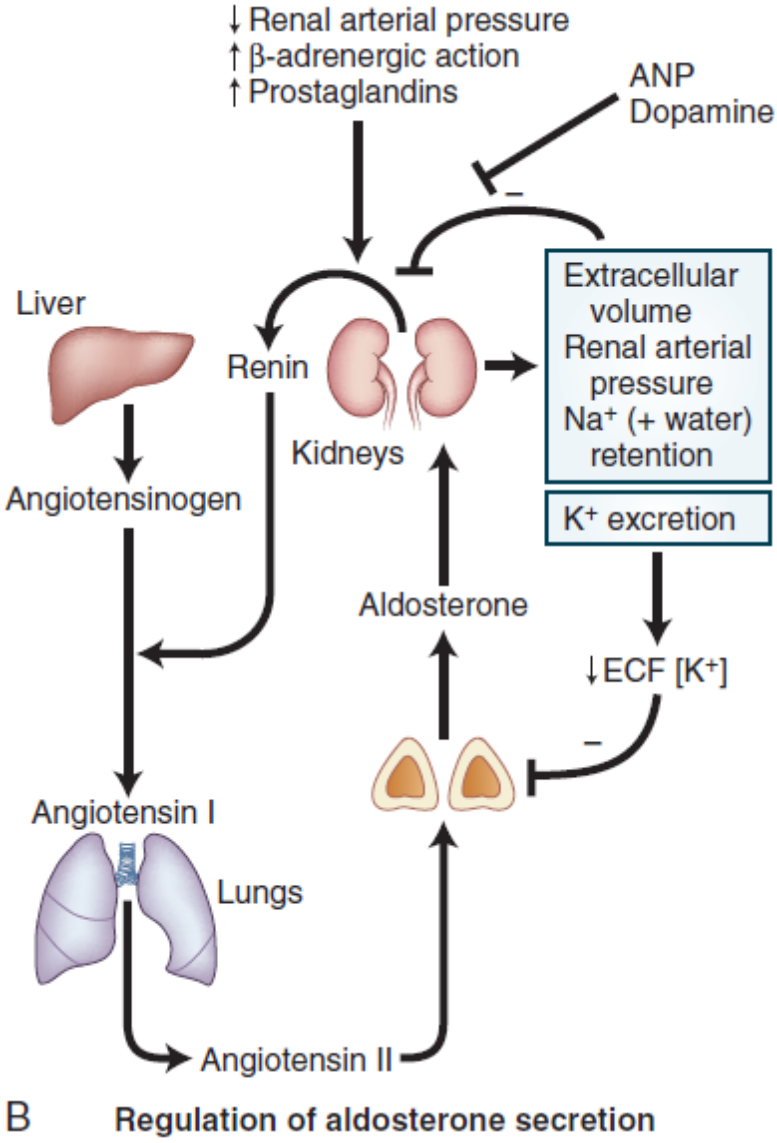
- **Metyrapone** inhibits cortisol synthesis of 11-hydroxylase
- **Ketoconazole** inhibits the early steps of steroidogenesis
- **Mitotane,** a derivative of an insecticide is an adrenolytic agent that is also effective for reducing cortisol
- **Etomidate** Given in cortisol excess
- **INDICATION-**

1. Very severe, overt Cushing's (e.g., difficult to control hypokalemic hypertension or acute psychosis)
2. Patients with metastasized, glucocorticoid-producing carcinomas
3. Ectopic ACTH syndrome, in which the tumor cannot be located

Mineralocorticoids

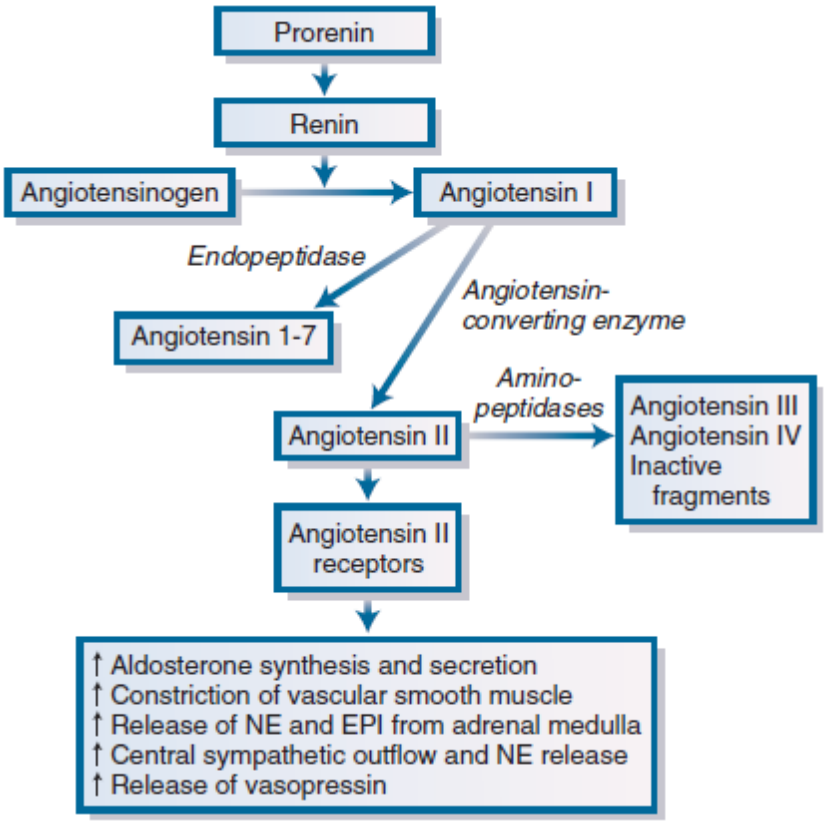
- The major mineralocorticoid - aldosterone, has two important actions: It is a major regulator of extracellular fluid volume and a major determinant of potassium metabolism. It stimulates the renal tubule to reabsorb sodium and excrete potassium, thereby protecting against hypovolemia and hyperkalemia. Aldosterone not only causes potassium to be secreted into the tubules in exchange for sodium reabsorption, but also causes secretion of hydrogen ions. This effect usually causes mild degree of alkalosis.
- When normal individuals are given aldosterone, an initial period of sodium retention is followed by natriuresis, and sodium balance is reestablished after 3 to 5 days. As a result, edema does not develop. This process is referred to as the escape phenomenon, signifying an "escape" by the renal tubules from the sodium-retaining action of aldosterone. While renal hemodynamic factors may play a role in the escape, the level of atrial natriuretic peptide also increases. However, it is important to realize that there is no escape from the potassium-losing effects of mineralocorticoids.
- The renin-angiotensin system controls extracellular fluid volume via regulation of aldosterone secretion. In effect, the renin-angiotensin system maintains the circulating blood volume constant by causing aldosterone-induced sodium retention during volume deficiency and by decreasing aldosterone-dependent sodium retention when volume is ample. Physiologic amounts of ACTH stimulate aldosterone secretion, but it is believed that ACTH has a minor role in the control of aldosterone.

- Potassium ion directly stimulates aldosterone secretion, independent of the circulating renin-angiotensin system, which it suppresses.



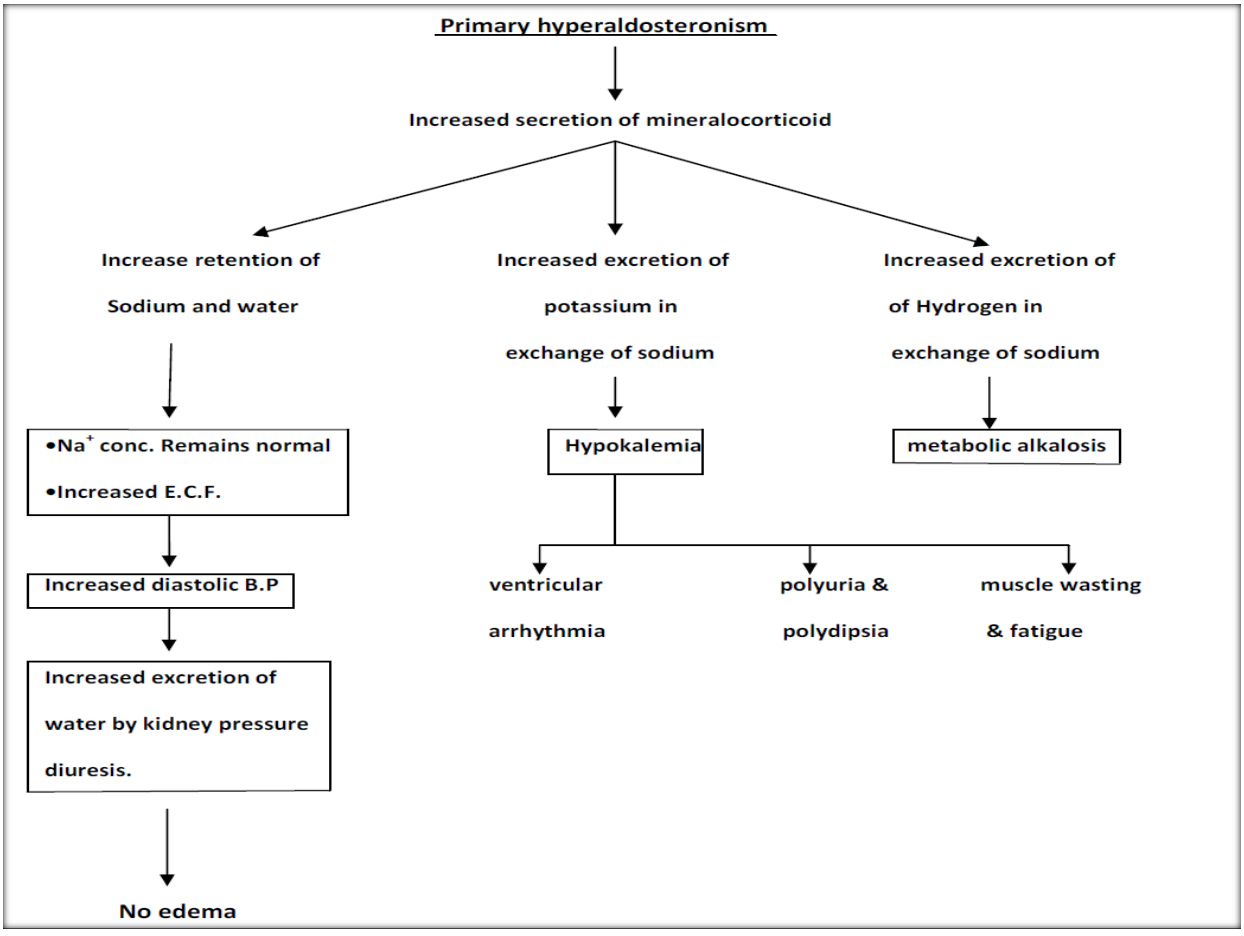
Renin-angiotensin-aldosterone system (RAAS)

Renin is secreted from the juxtaglomerular cells in the kidney dependent on renal arterial blood pressure. Renin converts angiotensinogen to angiotensin I, which is converted in the lungs by angiotensin converting enzyme (ACE) into angiotensin II. Angiotensin stimulates adrenal aldosterone synthesis. Extracellular fraction (ECF) of potassium has an important direct inhibitory influence on aldosterone secretion.



Components of Renin Angiotensin System

Causes of Mineralocorticoid Excess	Mechanism	%
Primary Hyperaldosteronism		
Adrenal (Conn's) adenoma	Autonomous aldosterone excess	40
Bilateral (micronodular) adrenal hyperplasia	Autonomous aldosterone excess	60
Glucocorticoid-remediable hyperaldosteronism (dexamethasone-suppressible hyperaldosteronism)	Crossover between the *CYP11B1* and *CYP11B2* genes results in ACTH-driven aldosterone production	<1
Other Causes (Rare)		<1
Cushing's syndrome		
Adrenocortical carcinoma		
Congenital adrenal hyperplasia		
Liddle's syndrome– Mutant ENaC β or γ subunits resulting in reduced degradation of ENaC keeping the membrane channel in open conformation for longer, enhancing mineralocorticoid action		



Primary hyperaldosteronism – (Signs and symptoms)

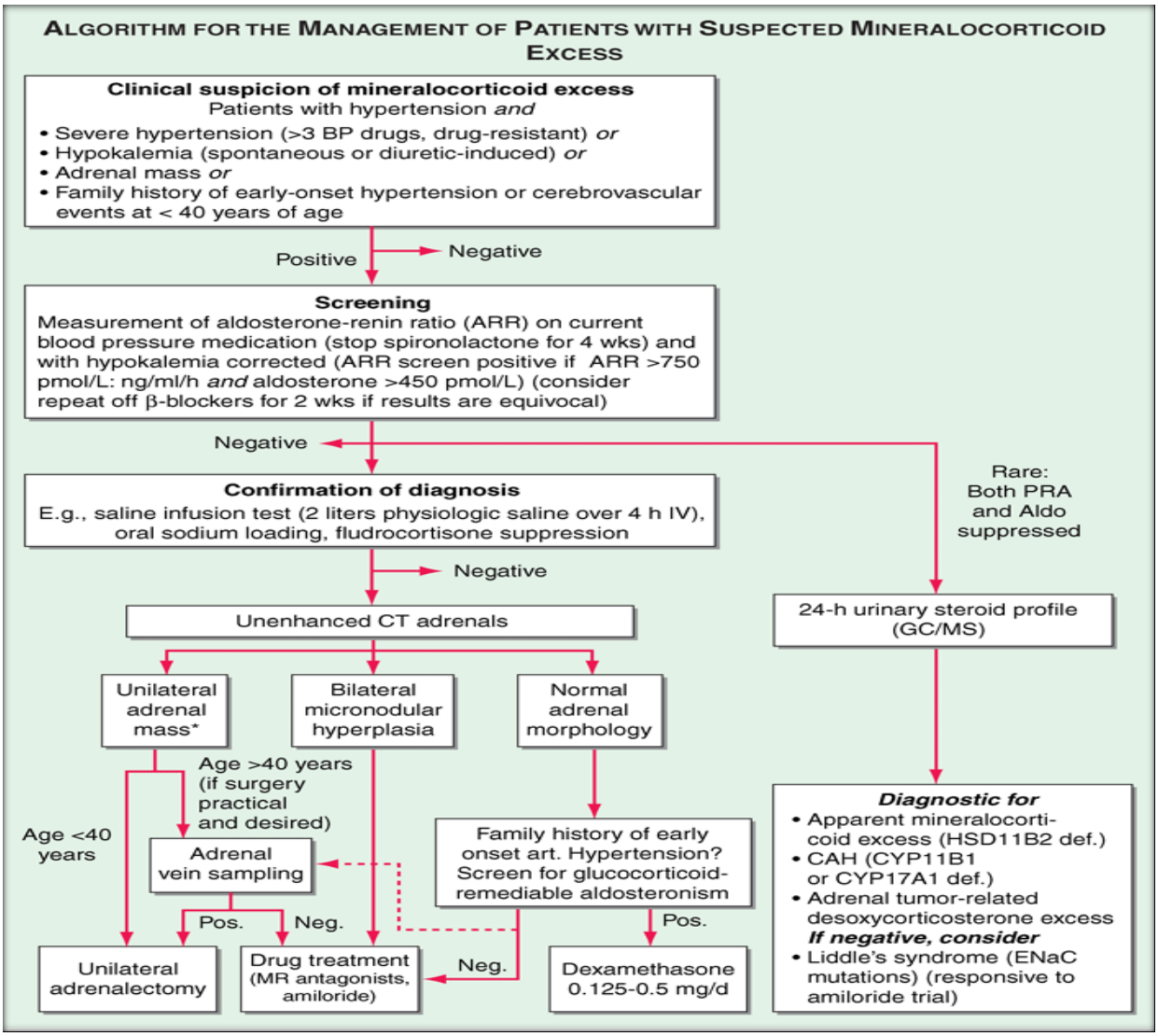
- Diastolic hypertension - produce headache without edema.
- Muscle weakness and fatigue due to the effect of potassium depletion on muscle cell membrane.
- Polyuria and polydipsia (due to impairment of urinary concentr.)
- Proteinuria occurs in 50% of patients.
- ECG signs of potassium depletion which includes prominent u waves cardiac arrhythmia and premature contractions.
- ECG and X ray signs of left ventricular failure.

Laboratory anomalies

- Hypokalemia
- Hypernatremia (infrequent, transient)
- Metabolic alkalosis

- **Aldosterone Renin Ratio (ARR) screening** - Positive if the ratio is more than 750 pmol/L: ng/mL per hour, with a concurrently high normal or increased aldosterone .
- **Diagnostic confirmation –**

- Saline infusion test,
- The oral sodium loading test
- Fludrocortisone suppression test



MEDICAL TREATMENT

INDICATION –

- Evidence of bilateral hyperplasia based on CT or AVS.
- Prior to surgery to avoid postsurgical hypoaldosteronism.
- Age more than 40 years with negative Adrenal vein sampling.
- glucocorticoid-remediable aldosteronism (GRA),
- *Liddle's syndrome.*

Treatment

- Mineralocorticoid receptor antagonist **spironolactone**. -- started at 12.5–50 mg bid and titrated up to a maximum of 400 mg/d to control blood pressure and normalize potassium.
- Selective MR antagonist **eplerenone** can also be used.
- Sodium channel blocker **amiloride (5**–10 mg/bid).
- For glucocorticoid-remediable aldosteronism (GRA)- **dexamethasone**, using the lowest dose to control BP.
- For*Liddle's syndrome*–
  - Very sensitive to **amiloride treatment**
  - Resistant to MR antagonist treatment, as the defect is due to a constitutively active ENaC.

Adrenal Insufficiency

Primary Adrenal Insufficiency	Secondary Adrenal Insufficiency
Autoimmune polyglandular syndrome 1 &2	Pituitary tumors
Congenital adrenal hyperplasia	Pituitary irradiation
Adrenoleukodystrophy (ALD), adrenomyeloneuropathy (AMN)	Pituitary apoplexy/hemorrhage
Familial glucocorticoid def..	Autoimmune hypophysitis
Adrenal infections, infiltration, hemorrhage	Pituitary infiltration, hemorrhage
Drug induced, surgery	Drug induced
Kearns–Sayre syndrome	

- Primary adrenal insufficiency is most commonly caused by autoimmune adrenalitis.
- Isolated autoimmune adrenalitis accounts for 30–40%,

- Whereas 60–70% develop adrenal insufficiency as part of autoimmune polyglandular syndromes (APS)
- APS-1 associated with Hypoparathyroidism, chronic mc candidiasis, other autoimmune disorders, lymphomas.
- APS-2 associated with Hypothyroidism, hyperthyroidism, Premature ovarian failure, vitiligo, type 1 DM, Pernicious anemia.
- Adrenal infections—by Tuberculosis, HIV, CMV, cryptococcosis, histoplasmosis, coccidioidomycosis.
- Adrenal infiltration —by Metastases, lymphomas, sarcoidosis, amyloidosis, hemochromatosis.
- Adrenal hemorrhage —by Meningococcal sepsis (Waterhouse-Friderichsen syndrome), primary antiphospholipid syndrome.
- Kearns-Sayre syndrome- Progressive external ophthalmoplegia, pigmentary retinal degeneration, cardiac conduction defects, gonadal failure, hypoparathyroidism, type 1 diabetes.

Adrenal insufficiency (Addison's disease)

Glucocorticoid deficiency	Mineralocorticoid deficiency	Adrenal androgen deficiency	Other signs and symptoms
Fatigue, wt loss	Abdominal pain	Energy loss	Hyperpigmentation (primary AI only) (due to excess of POMC derived peptides)
Fever	nausea, vomiting	Dry and itchy skin (women)	
Anemia, lymphocytosis, eosinophilia	Low BP, postural hypotension	Loss of libido(in women)	Alabaster–colored pale skin (secondary AI only) (due to deficiency of POMC derived peptides)
increased TSH	Salt craving	Loss of axillary and pubic hair (in women)	
Hypoglycemia (children)	Increased serum creatinine (due to volume depletion)		
Low BP, postural hypotension	Hyponatremia		
Hyponatremia	Hyperkalemia		

- due to lack of ACTH secretion. Chronic adrenal insufficiency – Manifested as

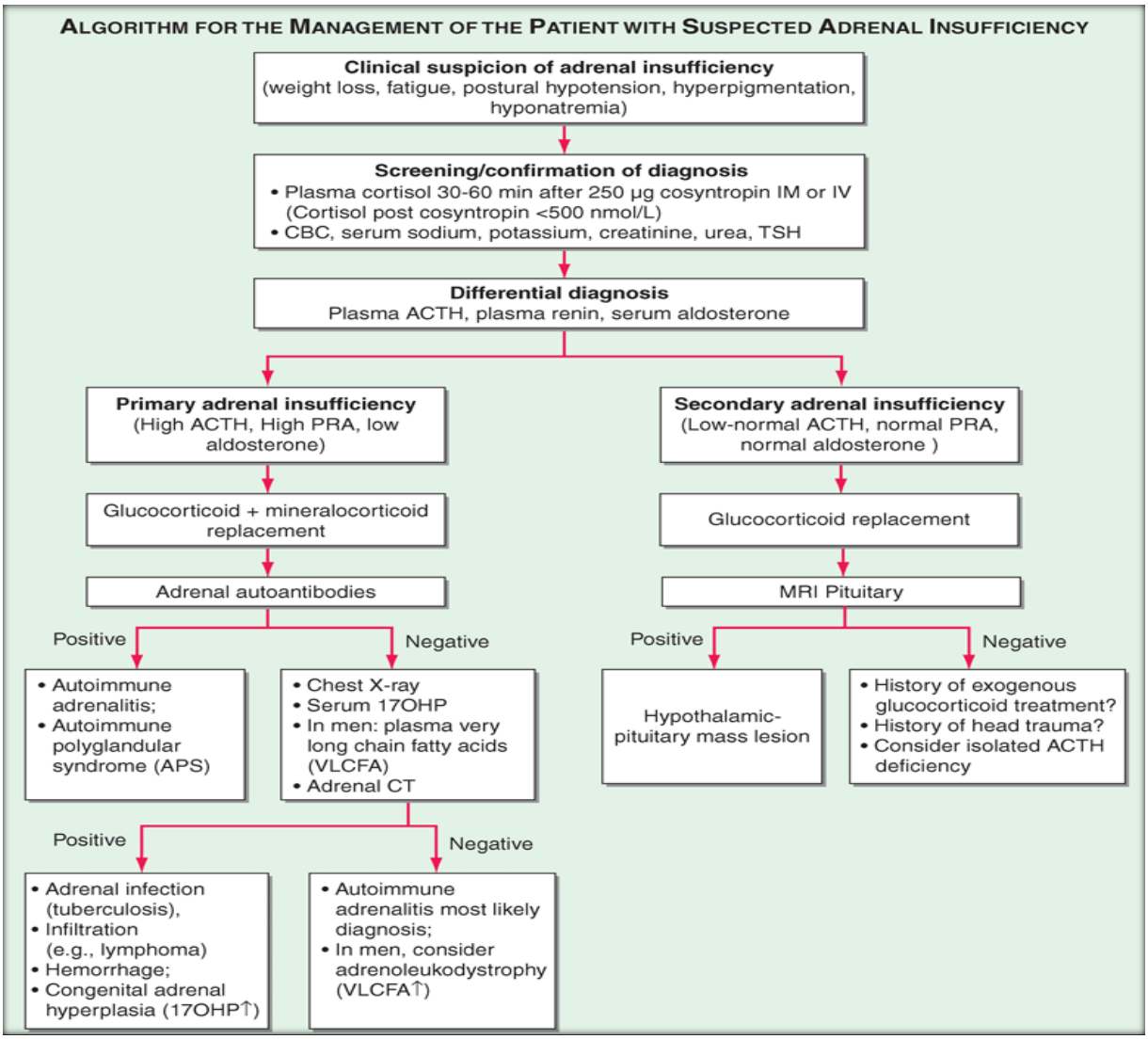
• *Fatigue and loss of energy,* often resulting in delayed or missed diagnoses (e.g., as depression or anorexia).

- In Primary adrenal insufficiency –
  - *Hyperpigmentation,* (caused by excess ACTH stimulation of melanocytes)
  - Hyperpigmentation is most pronounced in skin areas exposed to increased friction or shear stress and is increased by sunlight .
- In secondary adrenal insufficiency,
- Skin has an *alabaster-like paleness*

Acute adrenal insufficiency –

- More frequently observed in patients with primary adrenal insufficiency, due to the loss of both glucocorticoid and mineralocorticoid secretion.
- Postural hypotension may progress to hypovolemic shock.
- Adrenal insufficiency may mimic features of acute abdomen with abdominal tenderness, nausea, vomiting, and fever.
- In some cases, the primary presentation may resemble neurologic disease, with decreased responsiveness, progressing to stupor and coma.
- An adrenal crisis can be triggered by an intercurrent illness, surgical or other stress, or increased glucocorticoid inactivation (e.g., hyperthyroidism)

Lab finding of Addison's disease	
Hyponatremia	Na loss in urine (d/t aldosterone def..)
Hyperkalemia	d/t Aldosterone def.
Hypercalcemia	Seen in 10–20% of patients, unclear reasons
Hypotension	Aldosterone def. leads to loss of Na & water
Hypoglycemia	d/t glucocorticoid def..



Treatment

- **Acute Adrenal Insufficiency-**
- Immediate rehydration (by saline infusion at initial rates **of 1** L/h with continuous cardiac monitoring)
- Glucocorticoid replacement (by hydrocortisone bolus injection of 100 mg, followed by 100–200 mg/day).
- Mineralocorticoid replacement can be initiated once the daily Hydrocortisone dose has been reduced to < 50 mg because at higher doses hydrocortisone provides sufficient stimulation of mineralocorticoid receptors

Chronic adrenal insufficiency –

- Hydrocortisone – oral 15–25 mg in two to three divided doses.
- Half of the daily dose -administered in the morning.
- Pregnancy -hydrocortisone dose increases by 50% in last trim.
- Doubling the routine oral glucocorticoid dose – in intercurrent illness with fever
- IV hydrocortisone(100 mg)- in cases of prolonged vomiting, surgery, or trauma.
- ***Mineralocorticoid replacement*** in primary adrenal insufficiency -initiated at **100–150 g fludrocortisone**.

Treatment can be evaluated by

- measuring blood pressure, sitting and standing, to detect a postural drop indicative of hypovolemia,
- Also by serum sodium,potassium and renin level.
- *Adrenal androgen replacement* is an option in-
    - Patients with lack of energy,
    - In women with features of androgen deficiency, including loss of libido.
    - Adrenal androgen replacement can be achieved by once-daily administration of 25–50 mg DHEA

Congenital Adrenal Hyperplasia

- Patients affected by CAH exhibit glucocorticoid deficiency in all cases.
- Depending on the exact step of enzymatic block, they may-
    - Excess or less production mineralocorticoids
    - Deficient or over production of sex steroids.
- **Mutations in CYP21A2 –**
    - The most common cause of CAH (**90–95% of cases) —**

- Deficiency of glucocorticoid and mineralocorticoid,
- Overpoduction of sex steroids.

Female—

- severe virilization of the external genitalia in neonatal girls or
- hirsutism and oligomenorrhea.

Male-

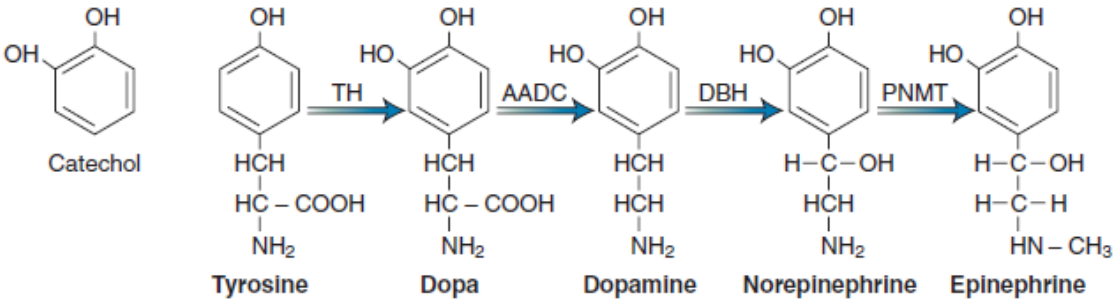
- A simple-virilizing genotype manifests with precocious pseudo-puberty and advanced bone age in early childhood.
- May present as adrenal insufficiency in the first few weeks of life (salt-wasting crisis);

Treatment

- Hydrocortisone for the prevention of adrenal crisis but longer-acting prednisolone may be needed to control androgen excess.
- In children, hydrocortisone is given in divided doses at 1–1.5 times the normal cortisol production
- In adults, intermediate-acting glucocorticoids (e.g., prednisone) may be given, using the lowest dose necessary to suppress excess androgen production.
- For achieving fertility, dexamethasone treatment may be required, but should be only given for the shortest possible time.
- Children with CAH usually receive mineralocorticoid and salt replacement.

PHEOCHROMOCYTOMA

- Mean age at diagnosis is about 40 years, although the tumors can occur from early childhood until late in life.
- The "rule of tens" –
  - 10% are bilateral
  - 10% are extraadrenal
  - 10% are malignant.



- However, these percentages are higher in the inherited syndromes.
- Normal adrenal medulla produces epinephrine(80%),norepinephrine(20%).
- In Adrenal PHEOCHROMOCYTOMA, Epinephrine is main hormone.
- In extra- adrenal PHEOCHROMOCYTOMA, Nor-epinephrine is main hormone.
- In Malignant PHEOCHROMOCYTOMA, besides epinephrine and norepinephrine,levels of dopamine and homovanillmic acid is increased.

Syndromes ass. With Pheochromocytoma—

About 25–33% of patients with a pheochromocytoma or paraganglioma have an inherited syndrome.

The mean age at diagnosis is about 15 years lower in patients with inherited syndromes compared with patients with sporadic tumors.

1. ***Von Hippel-Lindau syndrome (VHL)***is an autosomal dominant disorder that predisposes to retinal and cerebellar hemangioblastomas, which also occur in the brainstem and spinal cord .
2. MEN 2A and 2B.
3. *Neurofibromatosis type 1 (NF 1)* -multiple neurofibromas, café au lait spots, axillary freckling of the skin, and Lisch nodules of the iris .
4. *paraganglioma syndromes (PGL)—Ass.* with head and neck paragangliomas

CLINICAL FEATURES OF PHEOCHROMOCYTOMA

Effects of Catecholamines	Symptoms produced
CVS	**Hypertension**
•↑ in force of contraction •↑ in rate of contraction •↑ in peripheral resistance	•M.C. manifestation of pheochromocytoma •60% of the patients have sustained hypertension •40% have paroxysmal hypertension, Paradoxical response to antihypertensive drugs •d/t Sudden release of hormone from the neoplasm, ppt by bending (↑abd pressure) •accompanied by palpitations, tachycardia, feeling of anxiety and excess sweating
•↑ in myocardial excitability	**Arrhythmia**
	Sinus tachycardia Supraventricular arrhythmias VentricularPremature contractions
↑ in myocardial oxygen demand and coronary spasm	**Angina and myocardial infarction**, Dilated cardiomyopathy

Effects of catecholamines	Symptoms produced
On Basal metabolism	
↑ in metabolic rate	Profuse sweating Mild to moderate weight loss Elevated temperature
On carbohydrate metabolism	
Epinephrine have antiinsulin action, ↑ in glycogenolysis.	Impaired carbohydrate tolerance
Other manifestations :	
↓ in plasma volume	Elevated hematocrit
↓ in plasma volume and blunting of sympathetic reflexes	Orthostatic hypotension
other	Anxiety and panic attacks, pallor, nausea, Polyuria and polydipsia
Ectopic secretion of parathyroid hormone related proteins.	hypercalcemia

BIOCHEMICAL AND IMAGING METHODS USED FOR PHEOCHROMOCYTOMA AND PARAGANGLIOMA		
Diagnostic Method	**Sensitivity**	**Specificity**
24-h urinary tests		
Vanillylmandelic acid	++	++++
Catecholamines	+++	+++
Fractionated metanephrines	++++	++
Total metanephrines	+++	++++
Plasma tests		
Catecholamines	+++	++
Free metanephrines	++++	+++
CT	++++	+++
MRI	++++	+++
MIBG scintigraphy	+++	++++
Somatostatin receptor scintigraphy*	++	++
Dopa (dopamine) PET	+++	++++

Treatment

- Complete tumor removal is the ultimate therapeutic goal.
- Preoperative patient preparation is essential–
- Adrenergic blockers (**phenoxybenzamine**) should be initiated at relatively low doses (e.g., 5–10 mg orally three times per day) and increased as tolerated every few days.
- Because patients are volume-constricted, liberal salt intake and hydration are necessary to avoid orthostasis.
- Alpha blockade generally requires 7 days, with a typical final dose of 20–30 mg phenoxybenzamine three times per day.
- **Oral prazosin or intravenous phentolamine** can be used to manage paroxysms while awaiting adequate alpha blockade.
- Before surgery, blood pressure should be consistently below 160/90 mmHg, with moderate orthostasis.
- **Beta blockers** can be added **only after starting alpha blockers and increased as needed if tachycardia persists.**

- **Nitroprusside infusion -** useful for intraoperative hypertensive crises, and hypotension usually responds to volume infusion.

MULTIPLE ENDOCRINE NEOPLASIA (MEN) SYNDROMES			
	MEN 1	**MEN 2A**	**MEN 2B**
Pituitary	Adenomas, Hyperplasia	___	___
Parathyroid	Hyperplasia Adenoma	Hyperplasia or adenoma	___
Pancreatic islets	Hyperplasia Adenomas Carcinoma	___	___
Adrenal	Cortical hyperplasia	Pheochromocytoma	Pheochromocytoma
Thyroid	___	C-cell hyperplasia Medullary carcinoma	C-cell hyperplasia Medullary carcinoma
Extra-endocrine Changes	•Foregut carcinoid •Dermal angiofibroma or collagenoma	•Cutaneous lichen Amyloidosis •Hirschsprung disease	•Mucosal and GIT neuroma , •Ganglio-neuromas, •Marfanoid habitus
Mutant gene	MEN 1	RET	RET

Autosomal Dominant Syndromes Associated with Pheochromocytoma and Paraganglioma

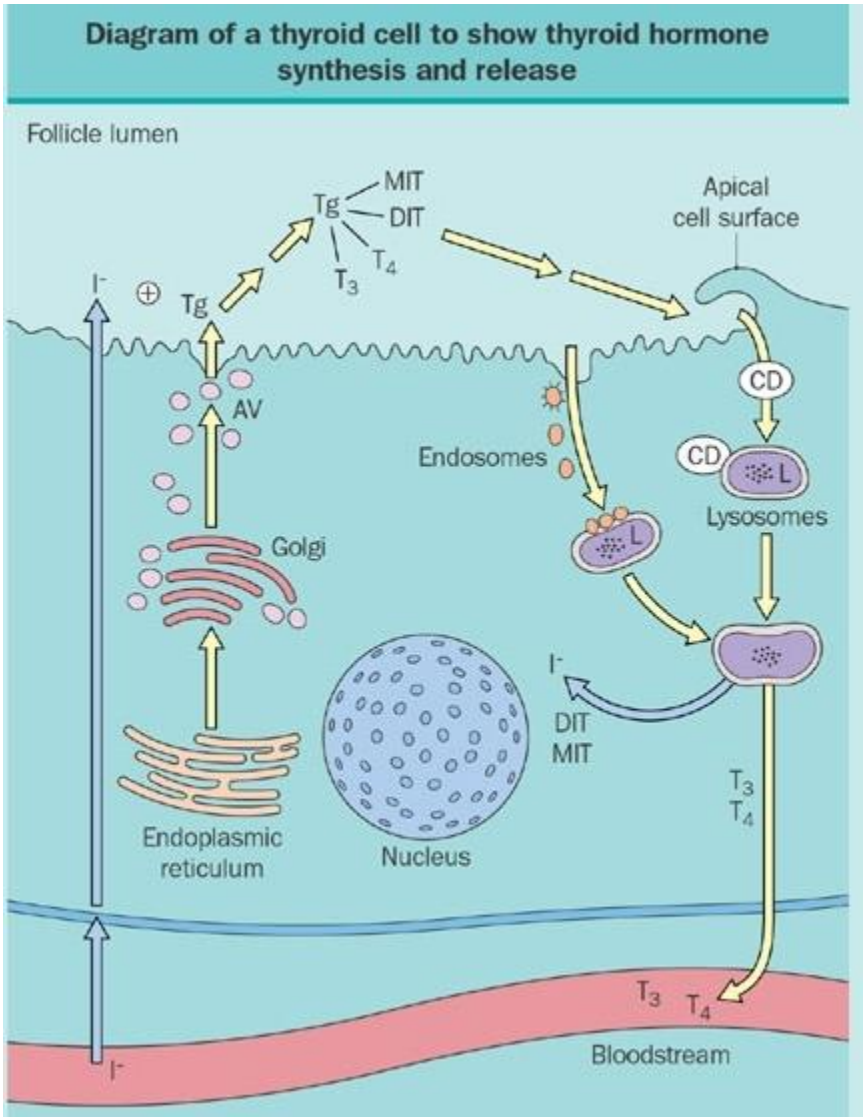
Syndrome	Gene	Gene Mechanism	Typical Tumor Location
SDHD (familial paraganglioma type 1)*	*SDHD*	Tumor suppressor	Skull base and neck; occasionally adrenal medulla, mediastinum, abdomen, pelvis
Familial paraganglioma type 2*	*SDHAF2*	Tumor suppressor	Skull base and neck; occasionally abdomen and pelvis
SDHC (familial paraganglioma type 3)	*SDHC*	Tumor suppressor	Skull base and neck
SDHB (familial paraganglioma type 4)	*SDHB*	Tumor suppressor	Abdomen, pelvis and mediastinum; rarely adrenal medulla, skull base, and neck
MEN1	*MEN1*	Tumor suppressor	Adrenal medulla
MEN2A and MEN2B	*RET*	Protooncogene	Adrenal medulla, bilaterally
Neurofibromatosis type 1	*NF1*	Tumor suppressor	Adrenal-periadrenal
von Hippel-Lindau disease	*VHL*	Tumor suppressor	Adrenal medulla, bilaterally; occasionally paraganglioma
Familial pheochromocytoma	*FP/TMEM127*	Tumo suppressor	Adrenal medulla

THYROID GLAND

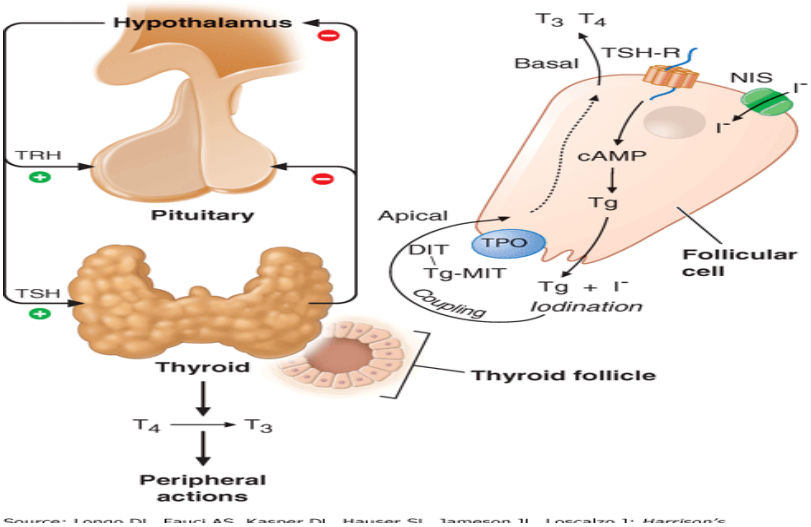
<u>Hormone Synthesis and Secretion-</u> 4 sequential steps (under the control of TSH)

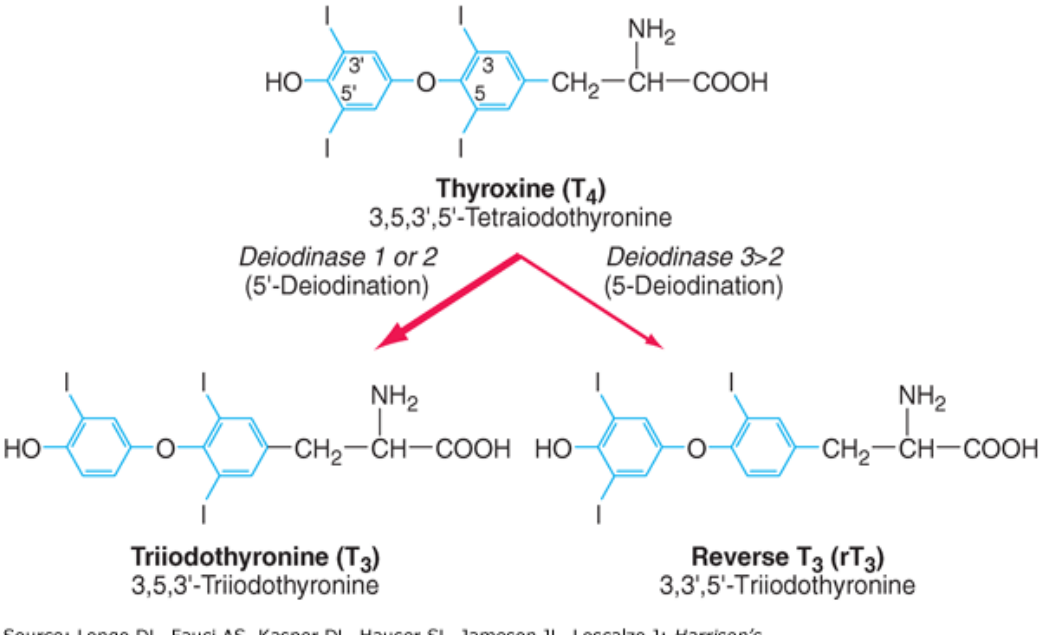
- **1st - active transport of iodide into the thyroid cell by NIS.**
- **2nd - oxidation of iodide to a higher-valenceform by a peroxidase.**
- **3rd -iodotyrosines** undergo **oxidative condensation** by same **peroxidase.**
- **4th - release of the free iodothyroninesT4 and T3 into the blood by protases.**

- Inactive iodotyrosines liberated by hydrolysis of thyroglobulin are stripped of their iodine by an intrathyroid enzyme, **iodotyrosine dehalogenase.**

- 

- ***Pendrin***, is located on the apical surface of thyroid cells and mediates iodine efflux into the lumen.
- Mutation of the PENDRIN gene causes **Pendred syndrome**, a disorder characterized by defective organification of iodine, goiter, and sensorineural deafness.





- Excess iodide transiently inhibits thyroid iodide organification, a phenomenon known as **Wolff-Chaikoff Effect.**
- In individuals with normal thyroid, the gland escapes from this inhibitory effect and iodide **organification** resumes;
- The suppressive action of high iodide may persist, however, in patients with ***underlying autoimmune thyroid disease.***

Regulation of the Thyroid Axis-

- **TSH stimulates** thyroid hypertrophy and hyperplasia;; stimulates the synthesis & secretion of thyroid hormones.

- **TRH** is the major positive regulator of TSH synthesis and secretion.
- **Free T3&T4** exhibit both positive & negative feedback both through TSH & TRH stimulation & inhibition respectively.
- **Dopamine, glucocorticoids, and somatostatin** suppress TSH.
- TSH excursions are modest **(single measurements of TSH are adequate for assessing its circulating level)**

Effects of Hormones on Thyroid Function
Glucocorticoids
Excess Decreased TSH, TBG, TTR (high-dose) Decreased serum T_3/T_4 ratio, increased rT_3/T_4 ratio Increased rT_3 production (? ↑ D3) Decreased T_4 and T_3 secretion in Graves' disease ***Deficiency*** Increased TSH
Estrogen
Increased TBG sialylation and increased half-life in serum Increased TSH in postmenopausal women Increased T_4 requirement in hypothyroid patients
Androgen
Decreased TBG Decreased T_4 turnover in women, reduced T_4 requirement in hypothyroid patients
Growth Hormone
Decreased D3 activity

D3, type 3 deiodinase; rT_3, reverse T_3; T_3, triiodothyronine; T_4, thyroxine; TBG, thyroxine-binding globulin; TSH, thyrotropin; TTR, transthyretin.

Hormone Transport, Metabolism & Action-

- T4 is bound in decreasing order of intensity to thyroxine-binding globulin (80%),to albumin (10%-30%) to a T4-binding prealbumin (transthyretin, 10%).
- **Only free hormone is available to tissues.**
- T4 is secreted from the thyroid gland in about twentyfold excess over T3, **the Fraction of unbound T3 is greater than unbound T4, because T3 is less avidly protein bound than T4 and there is T4 to T3 conversion in peripheral tissues**.

Characteristics of Circulating T_4 and T_3		
Hormone Property	**T_4**	**T_3**
Serum concentrations		
Total hormone	8 g/dL	0.14 g/dL
Fraction of total hormone in the free form	0.02%	0.3%
Serum half-life	7 d	0.75 d
Fraction directly from the thyroid	100%	20%
Intracellular hormone fraction	20%	70%
Relative metabolic potency	0.3	1

Abnormalities-

TBG levels are –

***Increased by* -estrogen, anti-androgens**

***Decreased in* -nephrotic syndrome and chronic liver disease**

- Mutations in various thyroid binding proteins may **increase binding affinity** for T4 or T3 to cause- **euthyroid hyperthyroxinemia** or **familial dysalbuminemic hyperthyroxinemia.**
    - ❖ **There is increased total T3 and T4 but unbound fraction remains normal.**
- **X linked TBG deficiency** is associated with low levels of total T4 and T3.
- However, patients are euthyroid and TSH levels are normal.
- Peripheral T4 to T3 conversion is impaired by variety of medications e.g. **propylthiouracil, propranolol, amiodarone, glucocorticoids.**

Effects of Pregnancy on Thyroid Physiology

Physiologic Change	Thyroid-Related Consequences
↑ Serum thyroxine-binding globulin	↑ Total T_4 and T_3; ↑ T_4 production
↑ Plasma volume	↑ T_4 and T_3 pool size; ↑ T_4 production; ↑ cardiac output
D3 expression in placenta and (?) uterus	↑ T_4 production
First-trimester ↑ in hCG	↑ Free T_4; ↓ basal thyrotropin; ↑ T_4 production
↑ Renal I^- clearance	↑ Iodine requirements
↑ T_4 production; fetal T_4 synthesis during second and third trimesters	
↑ Oxygen consumption by fetoplacental unit, gravid uterus, and mother	↑ Basal metabolic rate; ↑ cardiac output

D3, type 3 iodothyronine deiodinase; I^-, plasma iodide; hCG, human chorionic gonadotropin; T_3, triiodothyronine; T_4, thyroxine.

Thyroid Hormone Resistance-

- Autosomal dominant disorder with elevated thyroid hormone levels and elevated TSH.
- .Caused by mutations in the TR receptor gene.

LABORATRY EVALUATION-

- When a patient is suspected to have a thyroid disorder, **first test indicated is TSH (most sensitive).**
- If TSH is normal then **primary** thyroid disorder is unlikely.
- Measurement of **TSH and FT4** is enough to make the diagnosis of all cases of hypothyroidism and about 95% cases of hyperthyroidism.
- About 5% of thyrotoxic patients show elevation of FT3 alone known as Primary T3 thyrotoxicosis.

Type of disease	T4	T3	TSH
Conventional hyperthyroidism	Raised	Raised	Undetectable
T3-hyperthyroidism	Normal	Raised	Undetectable
Primary hypothyroidism	Low	Not indicated	Raised
Subclinical hypothyroidism	Normal	Not indicated	Raised
Secondary hypothyroidism	Low	Not indicated	Usually low
Secondary hyperthyroidism	Raised	Not indicated	Raised

.

AUTOIMMUNE ANTIBODIES-

- Autoimmune thyroid disease is detected by measuring circulating **antibodies against thyroid peroxidase and thyroglobulin**
- Patients with autoimmune hypothyroidism contain **Anti-TPO, Anti-TG and in some Anti-TSH Receptor (inhibitory) Antibodies.**
- *80 %* of Graves' disease patients have **anti-TPO antibodies**, antibodies against the TSH receptor stimulating it [thyroid-stimulating immunoglobulins (**TSI**)], and **anti-TG.**
- Measurements of the **serum thyroglobulin** by RIA have value **in assessing the adequacy of initial therapy and in monitoring for recurrence or dissemination of the thyroid carcinoma.**

Radioiodine Uptake and Thyroid Scanning

- Thyroid gland selectively transports radioisotopes of iodine (^{123}I, ^{125}I, ^{131}I) and ^{99m}Tc pertechnetate, allowing thyroid imaging and quantitation of radioactive tracer fractional uptake.
- The **RAIU varies directly with the functional state of the thyroid.**
- In the evaluation of solitary thyroid nodules, **fine-needle aspiration biopsy** has diminished the use of thyroid scan.

- But cold nodules, are usually benign. However, these nodules are more likely to be malignant (5–10%) than so-called **hot nodules, which are almost never malignant.**
- Thyroid scanning is also used in **the follow-up of thyroid cancer**.
- In this test, enlarged gland and **increased tracer uptake** characterize Graves' disease.
- Toxic adenoma appears as focal area of increased uptake, with suppressed tracer uptake in the remainder of the gland.
- In toxic multinodular goiter- shows multiple areas of decreased or increased tracer uptake.

Thyrotoxicosis is associated with a low RAIU-*thyrotoxicosis factitia, inadvertent ingestion of ground meat containing thyroid glands ("hamburger toxicosis"), and the spontaneously resolving thyrotoxicosis associated with postpartum thyroiditis or subacute thyroiditis.*

- Ultrasound-guided FNA biopsy – helps better sampling
- Used in the evaluation of recurrent thyroid cancer.

HYPOTHYROIDISM

- *Iodine deficiency* remains the most common cause of hypothyroidism worldwide.
- In areas of iodine sufficiency, *autoimmune disease and iatrogenic* causes are most common.

PRIMARY HYPOTHYROIDISM
Autoimmune hypothyroidism: Hashimoto's thyroiditis, atrophic thyroiditis
Iatrogenic: ^{131}I treatment, subtotal or total thyroidectomy, external irradiation
Drugs: iodine excess (including iodine-containing contrast media and amiodarone), lithium, antithyroid drugs,
Congenital hypothyroidism: absent or ectopic thyroid gland, dyshormonogenesis,
Iodine deficiency
Infiltrative disorders: amyloidosis, sarcoidosis, hemochromatosis,
TRANSIENT HYPOTHYROIDISM
Silent thyroiditis, including postpartum thyroiditis
Subacute thyroiditis
After ^{131}I treatment or subtotal thyroidectomy for Graves' disease
Secondary
Hypopituitarism: tumors, pituitary surgery or irradiation, infiltrative disorders, Sheehan's syndrome, trauma,
Hypothalamic disease: tumors, trauma, infiltrative disorders, idiopathic

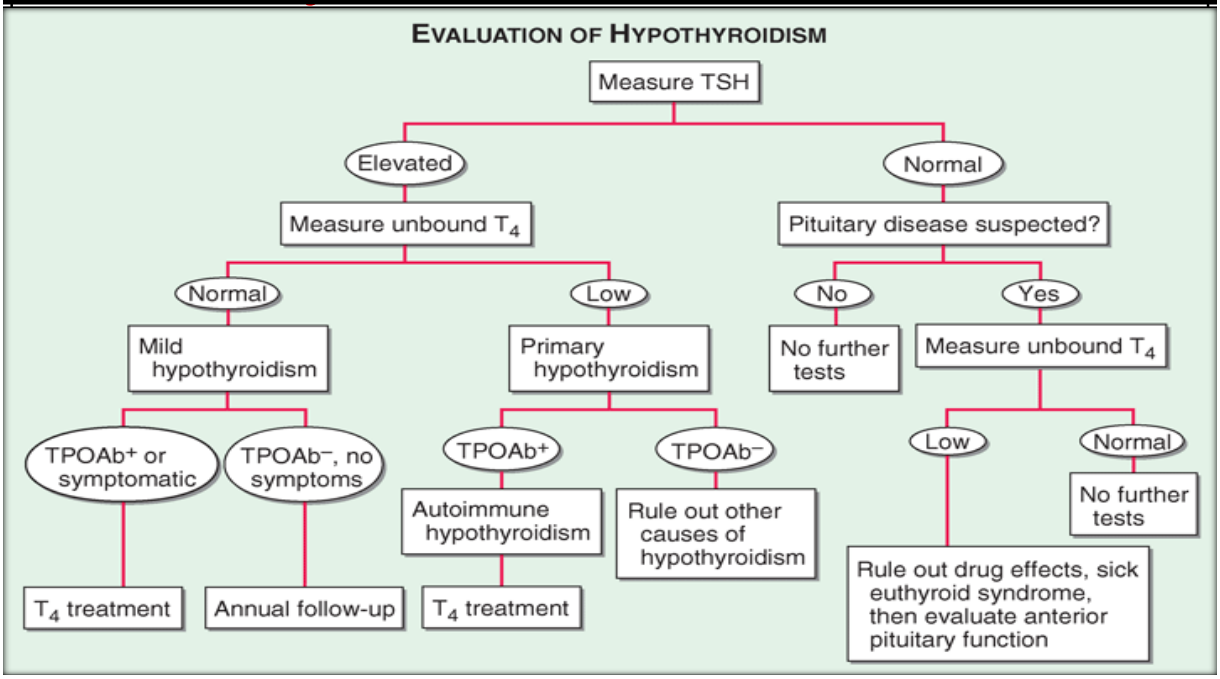
- **Goiter is frequently noted when hypothyroidism is due** to –

➢ Hashimoto’s thyroiditis, iodide deficiency, genetic enzyme defects and drug/food goitrogens.

- **Goiter is usually absent when hypothyroidism is due to –**

➢ Deficient pituitary TSH secretion, or destruction of thyroid gland by surgery, radioiodine or external radiation

Laboratory Evaluation



Signs and Symptoms of Hypothyroidism (Descending Order of Frequency)

Symptoms

- Tiredness, weakness
- Dry skin
- Feeling cold
- Hair loss
- Difficulty conc. and poor memory
- Constipation
- Weight gain with poor appetite
- Dyspnea
- Hoarse voice
- Menorrhagia (later oligomenorrhea or amenorrhea)
- Paresthesia
- Impaired hearing

Signs

- Dry coarse skin; cool peripheral extremities
- Puffy face, hands, and feet (myxedema)
- Diffuse alopecia
- Bradycardia
- Peripheral edema
- Delayed tendon reflex relaxation
- Carpal tunnel syndrome
- Serous cavity effusions

Autoimmune Hypothyroidism-

- Associated with a –
    - goiter (**Hashimoto's, or goitrous thyroiditis**) or,
    - Later stages of the disease, minimal residual thyroid tissue (**atrophic thyroiditis).**

PATHOLOGY-

- In Hashimoto's thyroiditis, there is **a marked lymphocytic infiltration ,**accompanied by **oxyphil metaplasia,surviving cell transferred into HURTHLE cell.**
- In atrophic thyroiditis, **the fibrosis is much more extensive, lymphocyte infiltration is less pronounced**, thyroid follicles are almost completely absent.
- Onset is usually insidious, **goiter which is usually painless**.
- First present with subclinical and then overt hypothyrodism.
- *Rare neurologic problems* include reversible cerebellar ataxia, dementia, psychosis, and myxedema coma.
- Hashimoto's **encephalopathy** has been defined as a steroid responsive syndrome associated with TPO antibodies, myoclonus, and slow-wave activity on EEG, not ass.with hypothyrodism.
- **TPO antibodies**, which are present in >90% of patients with autoimmune hypothyroidism.
- **FNAC** can be used to confirm the presence of autoimmune thyroiditis.

Other Causes of Hypothyroidism

- ***Iatrogenic hypothyroidism-*** In the first 3–4 months after radioiodine treatment, transient hypothyroidism may occur due to reversible radiation damage.
- Mild hypothyroidism after subtotal thyroidectomy may also resolve after several months, as the gland remnant is stimulated by increased TSH levels.

- **Iodine deficiency** is responsible for endemic goiter and cretinism but is an *uncommon cause of adult hypothyroidism unless* the iodine intake is very low .
- **Chronic iodide excess** can also produce *goiter and hypothyroidism*. Individuals with autoimmune thyroiditis are especially susceptible.
- This is seen in up to 15% of the patients treated with **Amiodarone**. **Lithium** (which, like iodide, inhibits the release of thyroid hormones can similarly cause hypothyroidism).
- Secondary hypothyroidism is usually diagnosed in the context of other anterior pituitary hormone deficiencies; **Isolated TSH deficiency is rare**.

TREATMENT OF HYPOTHYROIDISM-

- The synthetic hormone **levothyroxine** (L-thyroxine).
- Mostly a normal metabolic state **should be restored gradually**, ***especially in the elderly and in patients with heart disease***, since a sudden increase in metabolic rate may tax cardiac or coronary reserve.
- Initial daily dose of 50-µg levothyroxine can be increased by 25-50µg increments at 4-week intervals until a normal metabolic state is attained.
- In a ***healthy adult with no residual thyroid function***, starting dose of 100-150 µg is usually indicated.
- **Follow-up TSH measurement** is recommended at annual intervals.

Special considerations

- **Subclinical hypothyroidism** patients are treated if *the TSH level is >10mU/L and TPO antibodies are present* with low dose of **levothyroxine** in the range of 25-50 µg/d.
- In known or strongly suspected cases of **pituitary and hypothalamic hypothyroidism, thyroid replacement should not be instituted until treatment with hydrocortisone has been initiated**,.
- **Emergency surgeryis usually safe in patients with untreated hypothyroidism,** although routine surgery in a hypothyroid patient should be deferred until euthyroidism is achieved.

- Dose of thyroxin may need to be **increased by 50% or more during pregnancy** and returned to previous levels after delivery

Conditions That Alter Levothyroxine Requirements

Increased Levothyroxine Requirements
Pregnancy
Gastrointestinal Disorders
Mucosal diseases of the small bowel (e.g., sprue)
After jejunoileal bypass and small-bowel resection
Impaired gastric acid secretion (e.g., atrophic gastritis)
Diabetic diarrhea
Drugs That Interfere with Levothyroxine Absorption
Cholestyramine
Sucralfate
Aluminum hydroxide
Calcium carbonate
Ferrous sulfate
Drugs That Increase the Cytochrome P450 Enzyme (CYP3A4) Activity
Rifampin
Carbamazepine
Estrogen
Phenytoin
Sertraline
Drugs That Block T_4-to-T_3 Conversion
Amiodarone
Conditions That May Block Deiodinase Synthesis
Selenium deficiency
Cirrhosis
Decreased Levothyroxine Requirements
Aging (≥65 yr)
Androgen therapy in women

T_4, Thyroxine; T_3, triiodothyronine.

Myxedema Coma-

- If left untreated, the patient with long-standing hypothyroidism may pass into a **hypothermic, stuporous state that may be fatal.** This is called myxedema coma..
- It almost always occurs in elderly and is **usually precipitated by factors that impair respiration**, such as **drugs(sedatives, anesthetics, antidepressants), pneumonia, CHF and MI,UGI Bleeding,CVA.**

- Initial dose of **500 µg of levothyroxine** can be given as a single IV bolus or thru' the nasogastric tube. This should be followed by daily dose of 50-100 µg/day.
- Patients with myxedema coma and associated systemic illness may have a reduced ability to convert T4 to T3. Consequently, **supplementary doses of liothyronine** (T3) 10-25 microgram may be warranted.
- **Parenteral hydrocortisone** in the dose of 50 mg every 6h should also be given as there is an impaired adrenal reserve in profound hypothyroidism.
- Other **symptomatic treatment** should be given as needed (warming, antibiotics, correction of electrolytes,Ventilatory support,Treatment of precipitating factors, etc).

THYROTOXICOSIS

- denotes the clinical, physiologic, and biochemical findings when the tissues are exposed and respond to, excess thyroid hormone.
- Not synonymouswith hyperthyroidism, which is the result of excessive thyroid function.
- Thyrotoxicosis not associated with thyroid hyperfunction includes that associated with subacute thyroiditis and thyrotoxicosis factitia.
- In *subacute thyroiditis*, an excess of preformed hormone leaks from the gland owing to the presence of inflammatory disease. New hormone formation is decreased because of the suppression of TSH secretion by the hormone excess and, in some cases, because of the inflammatory injury itself.
- Thyrotoxicosis also occur when the source of excess hormone is outside of the thyroid gland, as in *thyrotoxicosis factitia*, the ingestion of meat contaminated with animal thyroids ("*hamburger toxicosis")*, the rare functioning *metastatic thyroid carcinoma, and struma ovarii*

Causes of Thyrotoxicosis

Primary hyperthyroidism
Graves' disease
Toxic multinodular goiter
Toxic adenoma
Functioning thyroid carcinoma metastases
Activating mutation of G_s (McCune-Albright syndrome)
Struma ovarii
Drugs: iodine excess (Jod-Basedow phenomenon)

Thyrotoxicosis without hyperthyroidism
Subacute thyroiditis
Silent thyroiditis
Other causes of thyroid destruction: amiodarone, radiation, infarction of adenoma
Ingestion of excess thyroid hormone (thyrotoxicosis factitia) or thyroid tissue
Secondary hyperthyroidism
TSH-secreting pituitary adenoma
Chorionic gonadotropin-secreting tumors[a]
Gestational thyrotoxicosis[a]

- In hyperthyroidism, hyperfunction of the thyroid is reflected in an **increased** RAIU.

- In nonhyperthyroid thyrotoxic states, thyroid function (as reflected in the RAIU) is **subnormal.**
- Treatment of thyrotoxicosis intended to decrease hormone synthesis (antithyroid agents, surgery, or radioiodine) is **appropriate** in hyperthyroidism .
- But it is **inappropriate** and **ineffective** in other forms of thyrotoxicosis.

GRAVES' DISEASE-

- 60–80% of thyrotoxicosis.
- Typically occurs between **20 and 50 years** of age;mainly in **females.**
- Due to combination of environmental and genetic factors, including polymorphisms in **HLA-DR3/DR4.**
- Is caused by **TSI antibodies** which can be detected by using the more widely available **TBII assays**.
- TPO antibodies occur in up to 80% of cases and serve as a readily measurable marker of autoimmunity.
- **Cytokines** appear to play a major role in thyroid-associated ophthalmopathy.

. ***Clinical Manifestations***

- The clinical presentation depends on

1. the severity of thyrotoxicosis,
2. the duration of disease,
3. individual susceptibility to excess thyroid hormone,
4. and the patient's age.

- In the elderly, --as ***apathetic thyrotoxicosis, sometime mistaken for depression.***

Signs and Symptoms of Thyrotoxicosis (Descending Order of Frequency

Symptoms

• Hyperactivity • Irritability •Dysphoria
•Heat intolerance and sweating,

• Palpitations, •Fatigue and weakness,
•Weight loss with increased appetite,

• Diarrhea, Polyuria, •Oligomenorrhea,
•Loss of libido

Signs

• Tachycardia; atrial fibrillation in the elderly
• Tremor

• Goiter, • Warm, moist skin,
• Muscle weakness,

• Proximal myopathy • Lid retraction or lag •
Gynecomastia

- In general, **nervous symptoms** dominate the clinical picture in **younger individuals, whereas cardiovascular and myopathic symptoms** predominate in **older .**
- There may be a thrill or bruit due to the increased vascularity of the gland and the hyperdynamic circulation

- ***Graves' ophthalmopathy-*** onset of Graves' ophthalmopathy occurs within the year before or after the diagnosis of thyrotoxicosis in 75% of patients but can sometimes precede or follow thyrotoxicosis by several years.
- Radioiodine treatment for hyperthyroidism worsens the eye disease in a small proportion of patients (especially smokers).
- Antithyroid drugs or surgery have no adverse effects on the clinical course of ophthalmopathy

NO SPECS

0 = **N**o signs or symptoms

1 = **O**nly signs (lid retraction or lag), no symptoms

2 = **S**oft-tissue involvement (periorbital edema)

3 = **P**roptosis (>22 mm)

4 = **E**xtraocular-muscle involvement (diplopia)

5 = **C**orneal involvement

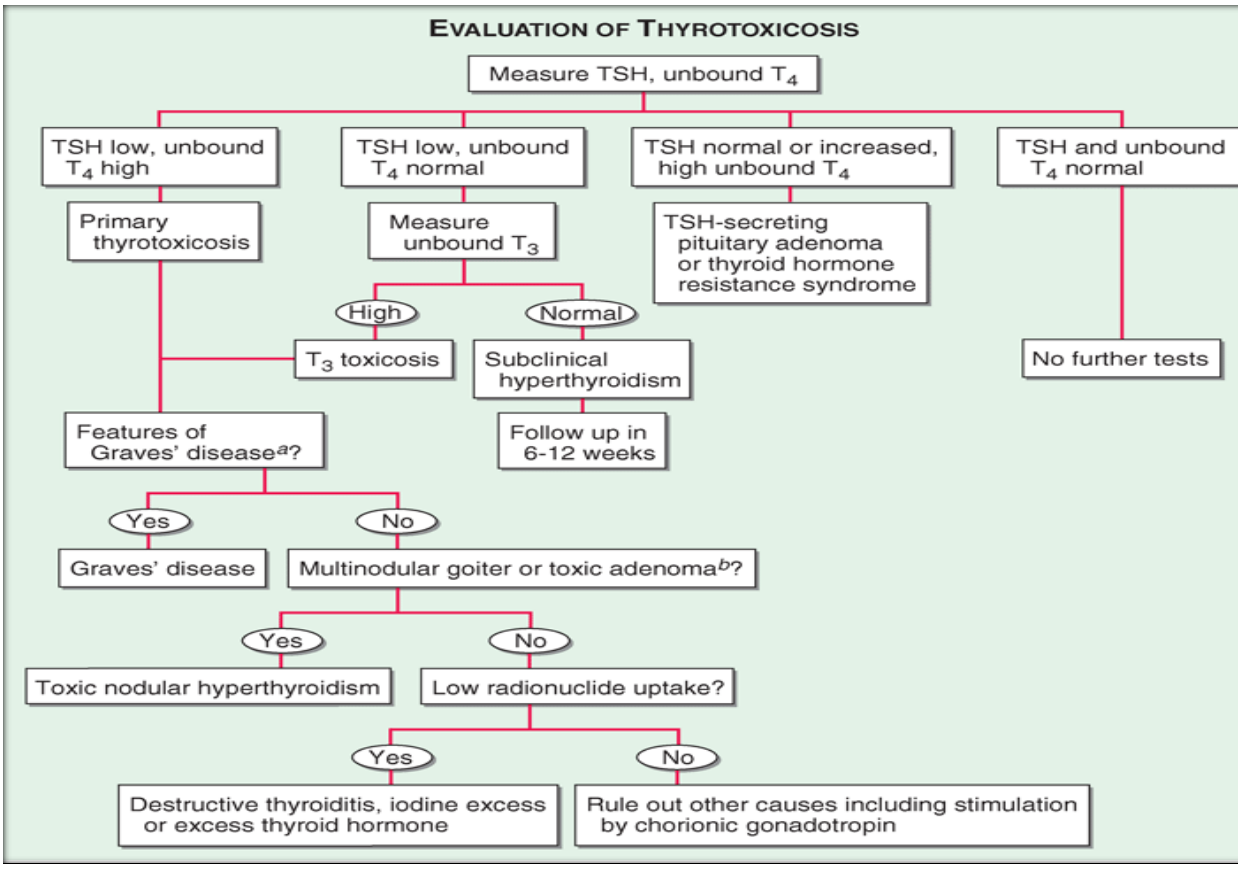
6 = **S**ight loss.

Thyroid dermopathy

- *Thyroid dermopathy* occurs in <5% of patients with Graves' disease almost always in the presence of moderate or severe ophthalmopathy.
- Although most frequent over the anterior and lateral aspects of the lower leg (hence the term ***pretibial myxedema***), skin changes can occur at other sites, particularly after trauma.
- ***Thyroid acropachy*** **-**clubbing.

<u>Diagnosis</u>

- Diagnosis of Graves' disease is straightforward in a patient with **biochemically confirmed thyrotoxicosis, diffuse goiter on palpation, ophthalmopathy, and often a personal or family history of autoimmune disorders**.
- For patients with thyrotoxicosis who lack these features, the **most reliable diagnostic method is to measure TBII or TSI.**
- An alternative is to undertake a radionuclide (^{99m}Tc, ^{123}I, or ^{131}I) scan of the thyroid, which will distinguish the diffuse, high uptake of Graves' disease from nodular thyroid disease, destructive thyroiditis, ectopic thyroid tissue, and factitious thyrotoxicosis.
- In secondary hyperthyroidism due to a TSH-secreting pituitary tumor, there is also a diffuse goiter. The presence of a nonsuppressed TSH level and the finding of a pituitary tumor on CT or MRI scan readily identify such patients.



Treatment

The ***hyperthyroidism*** of Graves' disease is treated

- by reducing thyroid hormone synthesis, using **antithyroid drugs,**
- or reducing the amount of thyroid tissue with radioiodine **(^{131}I) treatment or by thyroidectomy**
- A trial of long-term **antithyroid drug therapy** is desirable in **children, adolescents, young adults, and pregnant women**& in older patients.
- All antithyroid drugs **inhibit the function of TPO,** reducing the oxidation and organification of iodide.
- These drugs **also reduce thyroid antibodies** levels.

Incidence of Major Toxic Reactions to Anti-Thyroid Drugs in Adults

Side Effect	Frequency (%)	Comments
Polyarthritis	1-2	—
ANCA+ vasculitis	Rare	Mostly PTU
Agranulocytosis	0.1-0.5	May be more common with PTU
Hepatitis	0.1-0.2	PTU only
Cholestasis	Rare	Methimazole only

ANCA+, antineutrophil cytoplasmic antibody–positive; *PTU*, propylthiouracil.
Adapted from Cooper DS. Antithyroid drugs. *N Engl J Med.* 2005;352: 905-917.

- A commonly used regimen involves initial use of carbimazole in the dose of **10-20 mg twice or thrice a day,** which can be gradually reduced as the thyrotoxicosis improves.
- **Propylthiouracil** is given at a dose of 100–200 mg every 6–8 h,
- Thyroid function tests and clinical manifestations are reviewed 3–4 weeks after starting treatment, & the dose is titrated based on unbound T4 levels.
- ***Propranolol*** (20–40 mg every 6 h) or longer-acting beta blockers such as **atenolol,** may be helpful to control adrenergic symptoms, especially in the early stages before antithyroid drugs take effect.
- The need for anticoagulation with coumadin should be considered in all patients with atrial fibrillation.

Indications for ablative procedures include

- *relapse or recurrence following drug therapy,*
- *a large goiter,*
- *drug toxicity,*
- *failure to follow a medical regimen, or*
- *failure to return for periodic examinations*

Subtotal or near-total thyroidectomy may be elected for patients -

1. *under the age of 30 in whom ablative therapy is required,*
2. *in patients with very large goiters or*

3. *with a coincident nonfunctioning nodule, especially if there is a history of radiation to the head and neck.*

- Careful control of thyrotoxicosis with antithyroid drugs, followed by potassium iodide is needed prior to surgery to avoid **thyrotoxic crisis** and to reduce the vascularity of the gland.

Radioactive Iodine is the ablative procedure of choice in -

1. *older patients,*
2. *patients with previous thyroid surgery, and*
3. *those in whom systemic disease contraindicates elective surgery.*

- There is a small risk of thyrotoxic crisis after radioiodine, which can be minimized by pretreatment with antithyroid drugs for at least a month before treatment.
- **Ophthalmopathy** requires no active treatment when it is mild or moderate, as there is spontaneous improvement.
- Patients with *gritty sensations* may derive benefit from methylcellulose eye drops.
- *Corneal exposure during sleep* can be avoided by taping the eyelids shut.
- Severe ophthalmopathy with optic nerve involvement or chemosis resulting in corneal damage is an emergency.
- **Short-term benefit** can be gained in about two-thirds of patients by the use of **high-dose glucocorticoids** (e.g., prednisone, 40–80 mg daily), sometimes combined with **cyclosporine.**
- When glucocorticoids are ineffective, **orbital decompression done.**
- **External beam radiotherapy.**

OTHER CAUSES OF THYROTOXICOSIS-

- Destructive thyroiditis (**subacute and silent thyroiditis)** typically present with a ***short thyrotoxic phase*** **due to the release of preformed thyroid** hormones and catabolism of Tg. ***Circulating Tg levels are increased and RAIU is low.Ass.with painful goitre,ESR is Raised,Responds to NSAIDs,Antithyroid drugs not effective.***

- **Other causes of thyrotoxicosis with low or absent RAIU** include **thyrotoxicosis factitia** due to ingestion of excessive amount of exogenous thyroid hormone, and, thyrotoxicosis factitia can be distinguished from destructive thyroiditis by the clinical features and **low levels of Tg.**
- **Ectopic thyroid tissue**, particularly **stuma ovarii and functional metastatic follicular carcinoma**. **Whole body radionuclide studies** can demonstrate ectopic thyroid tissue.
- Iodine induced hyperthyroidism also called **Jodbasedow disease**, may occur in patients with **multinodular goiter** after intake of **large amount of iodine** in diet or in the form of radiographic contrast materials or drugs ***especially Amiodarone***
- **TSH-secreting pituitary adenoma** is a rare cause of thyrotoxicosis. It can be identified by the presence of an **inappropriately normal or increased TSH level in a patient with hyperthyroidism, diffuse goiter and elevated T4 and T3 lev**els. It can be confirmed by **demonstrating the pituitary tumor on MRI or CT.**
- Mild **gestational hyperthyroidism** may occur during the **first 4 months of pregnancy, when HCG levels are high.** Although HCG generally has low affinity for the thyroid's TSH receptors, very high serum levels of HCG may cause sufficient receptor activation to cause thyrotoxicosis.
- The high serum levels of HCG seen in **molar pregnancy, choriocarcimona and testicular malignancies** may also cause thyrotoxicosis

THYROTOXIC CRISIS-

- **A life-threatening exacerbation** of hyperthyroidism, accompanied by fever, delirium, seizures, coma, vomiting, diarrhea, and jaundice.
- The mortality rate due to cardiac failure, arrhythmia, or hyperthermia is as high as 30%, even with treatment.
- Thyrotoxic crisis is usually precipitated by acute illness (e.g., stroke, infection, trauma, diabetic ketoacidosis), surgery (especially on the thyroid), or radioiodine treatment of a patient with partially treated or untreated hyperthyroidism.
- **Supportive therapy** includes treatment of dehydration and the intravenous administration of glucose and saline, vitamin B complex, **and glucocorticoids**. antibiotics if infection is present, cooling, oxygen.

- Therapy of the hyperthyroidism consists of blockade of hormone synthesis by the immediate and continued administration of large doses of an antithyroid agent (e.g., 100 mg **propylthiouracil** every 2 h; drug's inhibitory action on conversion of T4 to T3 makes it the drug of choice.
- **One hour after the first dose Propylthiouracil, stable iodide is given** to block thyroid hormone synthesis via the **Wolff-Chaikoff effect.**
- **Adrenergic antagonists** – imp. & critical part of the therapeutic regimen in the absence of cardiac failure. Propranolol - given to reduce tachycardia and other adrenergic manifestations (40–60 mg PO every 4 h; or 2 mg IV every 4 h).

THYROIDITIS

Causes of Thyroiditis
Acute
Bacterial infection:
Fungal infection:
Radiation thyroiditis after ^{131}I treatment
Amiodarone (may also be subacute or chronic)
Sub-acute
Viral (or granulomatous) thyroiditis
Silent thyroiditis (including postpartum thyroiditis)
Chronic
Autoimmunity: focal thyroiditis, Hashimoto's thyroiditis, atrophic thyroiditis
Riedel's thyroiditis

SUBACUTE THYROIDITIS

- Also termed **granulomatous, giant cell, or de Quervain's thyroiditis**, is **viral** in origin. The peak incidence occurs at **30-50 years**, and **women** are affected **3 times** more frequently than men.

Clinical features

- Patient with **painful enlarged thyroid gland**, sometimes associated with fever. Symptoms *usually follow those of an upper respiratory infection* and include pain over the thyroid or the lower jaw, ear, or occiput.
- There may be **features of** thyrotoxicosis or hypothyroidism, depending on the phase.
- Physical findings include **exquisite tenderness and nodularity** of the thyroid, which may be unilateral but usually involves other areas of the gland.
- **High erythrocyte sedimentation rate (ESR) and a depressed RAIU.**
- The **TFTs characteristically evolve through 3 distinct phases** *over about 6 months:***thyrotoxic phase, hypothyroid phase and recovery phase.**
- TPO antibodies are **negative.**
- If diagnosis is in doubt, **FNA biopsy** may be useful, particular to distinguish unilateral involvement from bleeding into a cyst or neoplasm.

Treatment

- In mild cases - **aspirin** .
- In more severe cases - **glucocorticoids** (prednisone, 20 to 40 mg/d) .
- Associated thyrotoxicosis. **-Propranolol**
- **Antithyroid drugs play no role in the treatment of thyrotoxic phase.**
- Transient hypothyroidism is treated with **thyroxine if** symptomatic

SILENT THYROIDITIS –

- *Self-limited episode of thyrotoxicosis and clinically similar to subacute thyroiditis,*
- *except there is* **little or no thyroid tenderness.**
- **Features differentiating silent thyroiditis from subacute variety arepresence of TPO antibodies** (in low titer as compared to Hashimoto) &**normal ESR.**
- Severe symptoms can be managed with brief course of **propranolol.**

- **Glucocorticoid treatment is not indicated for silent thyroiditis.**
- **Thyroxine** replacement may be needed for the hypothyroid phase but should be withdrawn after 6-9 months, as recovery is the rule
- A variant of this after pregnancy is termed **postpartum thyroiditis**.
- This disorder develops within 2 to 6 months after delivery in 5 to 6 percent of otherwise normal women.
- Require symptomatic management with levothyroxine until the thyroid recovers.
- Women who become pregnant again are at risk for *recurrent postpartum thyroiditis*

REIDEL'S THYROIDITIS

- Rare disorder typically occurs in **middle-aged women**.
- Presents with **insidious, painless goiter with local symptoms due to compression of surrounding structures.** There is extensive infiltration of the thyroid and surrounding structures with **fibrous tissue**.
- Despite these changes, **thyroid dysfunction is uncommon.**
- It is a **manifestation of a multifocal systemic fibrosis syndrome,** with anterior neck symptoms predominating. Related conditions **include *retroperitoneal fibrosis, fibrosing mediastinitis, subretinal fibrosis and biliary tract sclerosis***.
- Diagnosis requires **open biopsy** as FNA biopsy is inadequate.
- Severe compressive symptoms might warrant a **surgical intervention.Tamoxifen** may also be beneficial.

SIMPLE (NONTOXIC) GOITER

- *Diffuse enlargement of the thyroid occurs **in the absence of nodules and hyperthyroidism.***
- More common in **women,** , most common cause is **iodine deficiency .**
- Diagnosis of I def.-Incresed TSH and Low urinary iodine levels **(< 100 µg/L)**

- Thyroid scanning is not generally necessary but will reveal **increased uptake in iodine deficiency and most cases of dyshormonogenesis.**
- ***Clinical manifestations--***arise from **enlargement of the thyroid**, since the metabolic state is normal.
- *Substernal goiter* may obstruct the thoracic inlet-- ***Pemberton's sign .***
- Respiratory flow measurements and CT or MRI should be used to evaluate substernal goiter in patients with obstructive signs or symptoms.
- **Hoarsenes and dysphagia are rare in simple goitre.**

Treatment—

- **Levothyroxine** is the agent of choice.
- In **the younger** patient, treatment is with **100** µg of levothyroxine daily,
- Dose is increased over the next month to a maximum of 150 or 200 µg/d.
- **Elderl**y patients should be initiated at **50 mcg/d.**

Surgical therapy—

- to relieve obstruction, or for cosmetic reasons. Subtotal or near-total **thyroidectomy** is surgery of choice.
- Large substernal goiters with partial upper airway obstruction also have been treated by ***radioactive iodine*** with moderate success

NONTOXIC MULTINODULAR GOITER–

- More common in iodine deficient areas.

• Common in **women** than men and increases **with age**.

- *Asymptomatic and* **always euthyroid.**

DIAGNOSIS-

- Thyroid architecture is distorted, and multiple nodules of varying size can be appreciated.
- **Pulmonary function testing, CT or MRI , barium swallow done to know obstructions.**

- **USG can be used to identify which nodules should be biopsied,.**

Treatment—

- T4 suppression is rarely effective for reducing goiter size .
- Contrast agents and other iodine-containing substances should be avoided because of the risk of inducing **the *Jod-Basedow effect***, characterized by enhanced thyroid hormone production by autonomous nodules.
- **Radioiodine- is possible to achieve a 40–50% reduction in goiter size in most patients,**
- **Surgery-2nd.choice.**

TOXIC MULTINODULAR GOITER=

- **The clinical presentation** includes subclinical hyperthyroidism or mild thyrotoxicosis.
- The patient **is usually elderly.**
- Thyroid scan shows heterogeneous uptake with multiple regions of increased and decreased uptake.

TREATMENT-Surgery provides definitive treatment.

- Radioiodine- not so
- Antithyroid drugs, often in combination with beta blockers, can normalize thyroid function, **in contrast to Graves' disease, spontaneous remission does not occur.**

HYPERFUNCTIONING SOLITARY NODULE (PLUMMER'S DISEASE)

- Referred as *toxic adenoma*.
- **Due to activating mutations in the TSH-R**
- A thyroid scan provides a definitive diagnostic test.

TREATMENT-

- **Radioiodine ablation – 1st choice**

- **Surgical resection-2nd choice.**.
- **Medical therapy** using antithyroid drugs and beta blockers can normalize thyroid function but is **not an optimal long-term treatment.**

THYROID NEOPLASMS-

- Most common malignancy of the endocrine system.

Differentiated tumors, such as papillary thyroid cancer (PTC) or follicular thyroid cancer (FTC), are often curable, and

- the prognosis is good if identified with early-stage disease.

In contrast, anaplastic thyroid cancer (ATC) is aggressive,

- responds poorly to treatment, and
- associated with a bleak prognosis

MALIGNANT TUMORS OF THE THYROID

Follicular epithelial cells	Well differentiated carcinoma • Papillary carcinoma (70%) • Follicular carcinoma (15%) Undifferentiated(anaplastic) carcinoma (5%)
C-cells or Parafollicular cells	Medullary thyroid cancer • Sporadic • Familial • MEN 2
Other malignancy	Lymphomas Sarcomas Metastasis

CTD

SYSTEMIC LUPUS ERYTHEMATOSUS

- M:F = 1:9 (mostly females of age 15-44)
- UV-B causes flares (sometimes A)
- Disease characteristically has period of remission and exacerbation

CLINICAL FEATURES

- Systemic symptoms (common to all CTD) : fever, fatigue, weight loss, anorexia
- Symmetrical, non – erosive arthritis + myopathy
- Alopecia
  - Scarring : DLE
  - Non-scarring : SLE
  - Scarring alopecia : loss, of hair follicles; so no regrowth
  - Non-scarring : shaft gone, hair follicles + regrowth
- Lupus nephritis
  - Who grading of kidney biopsy in SLE
    I – normal

    II – mesangial proliferative GN

III – focal proliferative GN

IV – diffuse proliferative GN

V – membranous proliferative GN

VI - ESRD

DPG: most serious lesion; wire – loop lesions + (subendothelial deposits, indicate active disease and poor prognosis)

- Pathogenesis : deposition of DNA – anti DNA complexes which form in situ
  The disease activity correlates with the titers of anti ds DNA antibodies

- Treatment : in general treatment for lupus nephritis is not recommended in patients with class I or II disease or with extensive irreversible changes. Aggressive immunesuppression is recommended for patients with class II, IV or V inflammatory proliferative lesions because the majority of those lesions if untreated develop end stage renal disease within 2 years.
- Prednisone 1 mg / kg body weight per day for 6 months cyclophosphamide 500 mg / m^2 – body surface area monthly for 6 months.

- **Nervous system**
  - MAJOR : seizures, major depression / psychosis, stroke, myelitis, peripheral neuropathy (SM : S>M), prolonged excruciating headache
  - Minor : mild occasional headache, mild depression, cognitive abnormality
- **Vascular system**
  Anti-phospholipid syndrome

Sapporo criteria

1. Recurrent arterial / venous thrombosis (without inflammation)
2. Recurrent fetal loss
3. Lupus anticoagulant (causes prolonged PTTK) / dilute Russels viper venom time
4. Anti-cardiolipin
5. Valvular heart disease
6. Thrombocytopenia

Patients with SLE who have venous or arterial clotting and / or repeated fetal loss and at least 2 positive tests for APLA have APS

Treatment: for patients with recurrent thrombosis warfarin is given in doses to maintain INR = 3.0

Peculiarity of APLAs: anti-coagulant in vitro, but pro-coagulant in vivo

- **Hematological manifestations**

- NCNC anemia (anemia of chronic disease) is the MC manifestation
- Other causes of anemia in SLE : AIHA, anemia due to renal failure
- DCT + ve in 30% pts
- But hemolytic and in only 10%
- Direct Coomb's abnormality on RBC memb.
- Indirect Coomb's abnormality in serum
- Thrombocytopenia
- Leucopenia
- Lymphopenia
- Treatment : prednisone 1 mg/kg per day for thrombocytopenia and hemolytic anemia

Cardiac lupus

- Pericarditis is the MC feature
- Libman sachs endovarditis
- AR, MR

Indications of steroids in cardiac lupus : heart failure, arrhythmias, embolic phenomena

PREGNANCY

Effects of SLE on pregnancy

- Spontaneous abortion / still birth (especially with APLS)
- Neonatal lupus, which can lead to heart block (due to transplacental transmission of maternal anti-Ro IgG)

Treatment for APLS in pregnancy (ie APLA and prior fetal loss)

- Injection heparin standard or low molecular weight and tablet aspirin 100 mg per day

Effects of pregnancy on SLE

- Disease flares in FEW patients
- Disease flares in puerperium

Treatment: prednisone or prednisolone at the lowest effective doses for the shortest time required.

Placental enzyme 11 β dehydrogenase 2 deactivates glucocorticoids. It is more effective in deactivating prednisone & prednisolone than the fluorinated glucocorticoids dexamethasoen & betamethasone.

DLE : scalp, ears, face : sun-exposed areas

- Circular lesions with raised, scaly, erythematous margins; with central atrophy & scarring

MED 5

Subacute cutaneous LE: dermatitis, arthritis, fatigue

- CNS, renal (-)

Antibodies related to SLE

Most sensitive antibody for SLE: ANA (98%)

Anti-dsDNA: associated with nephritis

Anti-Sm: specific for SLE

Anti-Ro : heart block, elderly, neonatal lupus, sjogren's ana – ve lupus

Anti-La: always assoc with anti-Ro; lower risk for nephritis

APLA include: lupus anticoagulant, anti cardiolipin, anti-β2 glycoprotein 1

ACR criteria (1992) for diagnosis of SLE

Malar rash : fixed rash, flat or raised over the malar eminences

Discoid rash : raised, scaling + atrophic scarring +

Photosensitivity exposure to UV light causes rash; the MC cutaneous manifestation

Ulcers : oral / nasopharynx ; usually painless

Arthritis : non-erosive arthritis of 2 or more peripheral joints with tenderness swelling or effusion

Serositis : pleuritis or pericarditis documented by ECG or rub or evidence of effusion

Renal disorder : proteinuria > 3 + or > 0.5 g/d or cellular casts

Neurological : serizures or psychosis without other cause

Hematological : hemolytic anemia, leucopenia, lymphocytopenia, thrombocytopenia

Immunological : anti-ds DNA / anti-Sm/ anti-phospholipid antibodies

ANA: by immunofluorescence

Treatment of SLE

Drug of choice for organ – or life-threatening SLE : steroids

- Indications for steroids in SLE
  GN, hemolytic anemia, (endocarditis, myocarditis), alveolar hemorrhage (hemoptysis), major CNS inv, thrombocytopenic Purpura, GI manifestations

- Steroids not given for:

Arthritis, fatigue, rash, leucopenia, anemia of chronic disease

Hydroxychloroquine

Reduces dermatitis, arthritis, fatigue

Decreases the frequency of exacerbations

NSAIDs in SLE

↑ rish of aseptic meningitis, transminemia, HT, renal dysfunction

RHEUMATOID ARTHRITIS

- Persistent inflammatory symmetrical arthritis of peripheral joints
- Characteristic joints : PIP, MCP, wrist, elbow : MTP, ankle, knee
- M:F = 1.3 (expect pleuropulmonary disease (M>F)
- 35-50 years
- Indians : HLA DR 1
- DRB1 * 0401 and DRB1 * 0404: associated with aggressive disease
- Cigarette smoking is a trigger
- Infection with EBV may be a trigger

Pathology

- Earliest lesion : synovitis
- CD4+ - th1 – IFN gamma – IL1 & TNF alpha – tissue destruction
  ±

- Th2 – IL4 (regulatory activity)
- Pannus = inflamed synovium
- Synovial fluid : exudates ; PMN > monocytes
- **synovial fluid WBC count > 2000/cmm with > 75% PMNs – INFLAMM ARTHRITIS (BUT NOT SPECIF IC FOR RA)

Clinical features

- Onset – 90% insidious : 10% acute
- Morning stiffness > 1 hour: improves with activity
  (c.f. degenerative arthritis i.e. OA, where stiffness with short periods of rest eg. sitting; and worsens with activity : morning stiffness not seen until disease is of few years duration, usually > 5 years)

Hand deformities

Z deformity / swan neck / boutoniere

Extraarticular features

- Rheumatoid nodules – 20-30% pts; extensor surfaces, peri-articular structures pleura, meanings, olecranon, Achilles tendon, occiput
- Methotrexate may increase no. of nodules
- Pleural effusion (M>F): low glucose in absence of infection
- Caplan syndrome : pneumoconiosis + pulmonary rheumatoid nodules
- Felty syndrome : RA + splenomegaly + neutropenia
- RA spares CNS ie, no direct involvement of CNS, except possibility of indirect cord compression due to cervical spine disease
- PNS: peripheral neuropathy due to rheumatoid vasculitis

Occasional features

- Carpal tunnel syndrome
- Baker's cyst: extension of inflamed synovium into popliteal space
- Axial INV : upper cervical spine (-- cord compression)
- Osteoporosis
- Eye- kerato-conjunctivits sicca, episcleritis, scleritis

Laboratory findings

Rheumatoid factor

- Anti-(Fc) IgG antibody
- Most tests detect IgM (both IgM & IgG +)
- 2/3rd pts
- Not specific for RA
- Not diagnostic
- Not useful for screening

- Prognostic significance because patients with high titers tend to have more severe & progressive disease with extra articular manifestations
- 5% of healthy individuals
- False +ve : SLE, sjogrens, chronic liver disease, interstitial pulmonary fibrosis, sarcoidosis, infectious mononucleosis, hepatitis B, TB, leprosy, syphilis, SABE, visceral leishmaniasis, malaria

Hematologic:

- Normocytic normochromic anemia
- Felty syndrome : chronic RA + splenomegaly + neutropenia
- Associated with large B – cell lymphoma

Radiological findings in RA

- Early disease : soft tissue swelling + effusion
- Weeks : juxta – articular osteopenia
- Months : cartilage destruction, bone erosion

Assessment of disease activity:

1. ESR
2. Synovitis (warmth, tenderness, joint pain)
3. Constitutional features
4. Radiology bone erosion / cartilage destruction

Diagnostic criteria by ACR

1. Morning stiffness – stiffness in & around the joints lasting 1 hour before maximal improvement
2. Arthritis of 3 or more joint areas
3. Arthritis of hand joints
4. Symmetric arthritis
5. Rheumatoid nodules
6. Serum rheumatoid factor
7. Radiographic changes

   First 4 criteria must be present for at least 6 weeks

   For diagnosis minimum 4 criteria should be present in a patient

Treatment of RA

DMARDs

MED 5

Methotrexate

Mechanism : inhibition of DHF Reductase

Leucovorin used for rescue of normal cells

Toxicity : GI mucosal irritation, BM suppression, pulmonary fibrosis, fatty liver

Others : gold, penicillamine, sulfasalazine, hydroxychloroquine,

LEFLUNOMIDE

Dihydro-orotase dehydrogenase inhibitors – inhibits pyrimidine synthesis

Adverse effects : hepatitis, alopecia

TNF α BLOCKERS

1. Infliximab : chimeric human / mouse monoclonal antibody
2. Etanercept : TNF alpha type II receptor + IgG1
3. Adalimumab

Adverse effects include increased risk of serious infections, pancytopenia, demyelinating disorders, exacerbation of CHF, SLE, hypersensitivity reactions and increased risk of malignancy.

IL-1 RECEPTOR BLOCKERS : ANAKINRA

SCLERODERMA

Diffuse cutaneous disease	Limited cutaneous disease (CREST syndrome)
Proximal + distal extremities, face, trunk	Distal extremities, face (spares prox ex)
Organ inv early : IPF, renovascular HT	Late (> 10 y) : pulm arterial HT, biliary cirrhosis
Antibodies anti-topoisomerase I (Scl 70)	Anti-centromere

* Sine scleroderma : visceral involvement without skin involvement

* Drugs : pentazocine, bleomycin

** Exposure to polyvinyl chloride (PVC): Raynaud's phenomenon, acro-osteolysis, scleroderma, pulmonary fibrosis, ungula telangiectasis, hepatic fibrosis, hepatic angiosarcoma

Antibodies associated and their significance

Anti-RNA polymerase I, II, III: diffuse cutaenous disease

Anti-Th RNP: limited cutaneous disease

Anti-U1 RNP:MCTD, limited cutaenous disease

Anti-U3 RNP: diffuse & limited ctuaneous disease, skeletal myopathy, PAH

Anti-PM/Scl: SSc, polymyositis overlap

Drugs useful for Raynaud's phenomenon:

-Nifedipine, diltiazem, amlodipine, sildenafil, losartan, ketansirin pentoxifyline.

Drugs for PAH:

-Nifedipine, diltiazem, amlodipine, iloprost, epoprostenol (PGI20, bosentan

Renal hypertensive crisis : ACE inhibitors

Skin thickening : D-pencillamine

SJOGREN'S SYNDROME

- It is a chronic, slowly progressive autoimmune disease characterized by lymphocytic infiltration of the exocrine glands resulting in xerostomia and dry eyes. The disease can be seen alone (primary sjogren's syndrome) or in association with other autoimmune disease.
- Association : Rheumatoid arthritis, SLE, scleroderma, MCTD, primary Biliary cirrhosis, chronic active hepatitis, vasculitis

- Middle aged females
- M:F = 1:9
- Slow, benign course
- Lymphoma : develops in few: marginal zone B cell: extranodal; MC SITE : SALIVARY GLAND
- Atrophy of filiform papillae : enlargement of salivary glands in primary sjogren (rare in secondary)
- Schirmer I test (+ve : < 5mm in 5 min)
- Antibodies to Ro / La (SS-A/ SS-B)
- Renal disease : interstitial nephritis, type I RTA, glomerulonephritis is rare.

Diagnostic criteria

1. Ocular symptoms
2. Oral symptoms
3. Ocular signs (shirmer's test, rose Bengal score)
4. Histopathology of salivary glands
5. Objective evidence of salivary gland involvement
6. Antibodies to Ro/SS –A or La/SS-B
   - 4 out of 6 criteria as long as no. 4 or no. 6 is positive
   - Any 3 out of 4 objective criteria items i.e. no 3,4,5,6

Treatment

- Xerostomia; water
- Artificial tears methylcellulose for dryness of eyes
- Hydroxychloroquine for arthralgia
- Patients with RTA should receive sodium bicarbonate orally

HIV + sicca syndrome

- Young males
- Ro / La-
- CD8 + infiltration of salivary glands
- HLA – DR 5

ANKELOSING SPONDYLITIS

Definition

Ankylosing spondylitis is a chronic inflammatory disease that causes arthritis of the spine and hips. It can also affect other joints such as the knees, and can cause inflammation of the eyes, lungs, or heart valves.

Pathology

- Enthesitis – enthuses : site of soft tissue (tendinous / ligamentous) attachement to bone

Clinical features

- M:F = 3:1
- Onset at 15-25 years
- 1st manifestation : sacroilitis
- Early inv of SI joint – lower lumbar spine – ascending progression – upper spine is involved late
- Morning backache with stiffness – improves with activity
- In months – persistent pain
- Nocturnal pain
- Constitutional features in few pts & elderly pts
- Peripheral joint inv in 30% pts; usually asymmetrical\
- Profile in developing countries (India)
    - Earlier (juvenile) onset
    - Early peripheral arthritis
    - Axial symptoms later than peripheral
    - HLA – B27

Radiological features

- Squaring of vertebra
- Syndesmophytes : new bone in outer layers of inter vertebral discs
- Pseudowidening bony ankylosis (bamboo spine)
- Osteoporosis

Extra articular diseases in AS

Acture anterior uveitis (M extra – articular manifestation) complications of recurrent attacks : papillary synechiae, cataract, secondary glaucoma

Aortic regurgitation: 3rd degree heart block

Inflammatory bowel disease

IgA nephropathy

Modified new York criteria – used for diagnosis

Presence of radiographic sacroiliitis plus any 1 of the following

1. History of inflammatory back pain
2. Limitation of lumbar spine movement
3. Limited chest expansion

Monitoring progress of disease

1. Height
2. Chest expansion
3. Schober test
4. Occiput to wall distance

Poor prognostic factor : early severe hip inv

Disease progresses very slowly in females

Complications

Spine fracture, cauda equine syndrome, upper lobe lung fibrosis

Treatment

TNF α antagonists are the most effective drugs

Sulfasalazine

Indomethacin

Steroids are not useful

BEHCET'S SYNDROME

Diagnostic criteria

- Recurrent oral ulcers + any 2 of

1. Recurrent genital ulcers
2. Eye involvement
3. Skin involvement
4. Pathergy test

- Young adults
- Males have more severe disease
- Vasculitis – venous thrombosis
- Autoantibodies to human oral mucosa

- HLA B5 (B51)

EYE

Most feared complication is bilateral pan uveitis because it rapidly progresses to blindness

Hallmark is hypopyon uveitis (THOUGH RARE)

Iritis, posterior uveitis, ON, RAO, RVO

Skin

-Folliculitis, erythema nodosum, acne

-Pathergy test : nonspecific dermal inflammatory response to scratching / intradermal saline injection

Rarely : CNS, arthritis, GI involvement

Neurological involvement appears mainly in the parenchymal form associated with brainstem involvement and has a serious prognosis; dural sinus thrombi may occur

Treatment

- Glucocorticoids
- Azathioprine
- Thalidomide for intractable aphthous ulcers
- * Early initiation of azathioprine improves the natural history of Behcet's syndrome

VASCULITIS SYNDROMES

POLYARTERITIS NODOSA (PAN)

- Multisystem disorder
- Involves medium sized arteries
- MC system : musculoskeletal > renal
- The vascular lesion in PAN is necrotizing inflammation of small & medium – sized arteries, the lesions are segmental & involve bifurcations and braches of arteries
- Aneurismal dilatations up to 1 cm in size along the involved arteries are characteristic of PAN
- Granulomas & eosinophilia are not found

- Pulmonary arteries are not involved, and bronchial artery involvement is uncommon
- The pathology in kidney is arteritis without glomerulonephritis
- Renal disease manifests as hypertension and renal failure
- Hepatitis B antigenemia in 10-30% of patients, antibodies against Hepatitis C virus in 5% and hairy cell leukemia can be associated with classic PAN
- Fever, weight loss, malaise are present in > 50% of cases
- Renal involvement most commonly presents as hypertension, renal insufficiency, or hemorrhage due to microaneurysms
- There are no diagnostic serologic tests for PAN ; ANCA are rarely found in classic PAN
- Diagnosis: biopsy of the involved organs shows characteristic findings of vasculitis ; angiography reveals aneurysms of small & medium sized arteries in the renal, hepatic, and visceral vasculature
- Treatment : prednisone in combination with cyclophosphamide
- Prognosis is extremely poor; with a 5 years survival rate between 10 & 20% death most commonly occurring from GI complication particularly bowel infarcts and perforations

MICROSCOPIC POLYANGITIS

- The vascular lesion is histolgically similar to classic PAN
- Unlike PAN, the vasculitis involves capillaries & venules in addition to small & medium sized arteries
- GN is very common, and pulmonary capillaritis often occurs; the absence of granulomatous inflammation differentiates it from Wegener's granulomatosis
- Onset : 50 years, males are slightly more commonly affected than females
- Constitutional symptoms are typically present
- Signs / symptoms of vascular occlusion in various organ systems
- P ANCA present in microscopic PAN
  - Target for p ANCA : myeloperoxidase
  - Target for c ANCA : proteinase 3
- Diagnosis : histologic evidence of vasculitis or pauci – immune glomerulonephritis in a patient with compatible clinical features of multi-system disease
- Treatment : prednisolone + cyclophosphamide (2mg/kg/d)
- Prognosis : mortality occurs primarily from alveolar hemorrhage or GI, cardiac or renal disease

CHURG STRAUSS SYNDROME

- Also known as allergic angiitis and Granulomatosis
- Mean age of onset is 48 years with F/M ratio as 1:2:1
- Pathogenesis: necrotizing vasculitis involving small and medium – sized muscular arteries, capillaries, veins, and venules, granulomatous reactions may be present in the tissues or even in the wall of the vessels.
- Fever, malaise, anorexia, weight loss
- Pulmonary findings dominate the clinical picture with severe asthmatic attacks & presence of pulmonary infiltrates
- Mononeuritis multiplex is the second MC manifestation
- Allergic rhinitis, sinusitis, skin lesions are common
- Heart disease and renal disease can occur
- Eosinophilia is common (AEC>1000/mm3); p ANCA is present in half the cases

- Diagnosis : biopsy of the involved tissues
- Treatment : steroids + cyclophosphamide
- Prognosis : 5-year survival is 25%; the MC cause of death is myocardial involvement
- Montelukast therapy may unmask / precipitate churg strauss syndrome

WEGENER'S GRANULOMATOSIS

- It is characterized by granulomatous vasculitis of the upper & lower respiratory tracts together with glomerulonephritis
- Mean age – 40 years M/F ratio is 1:1
- Necrotizing vasculitis of small arteries & veins together with granuloma formation, which may be intra or extra vascular
- Lung involvement typically appears as multiple, bilateral, nodular cavitary infiltrates
- Renal involvement is characterized by a focal and segmental glomerulitis that may evolve into a rapidly progressive crescentic glomerulonephritis. Granuloma formation is rare is kidney lesions and immune complex deposition is not seen.
- Upper airways involvement is seen in 95% cases. Nasal septal perforation may occur causing saddle nose deformity
- Pulmonary involvement may be manifested as asymptomatic infiltrates or may be clinically expressed as cough, hemoptysis, dyspnea, and chest discomfort
- Renal disease is the MC cause of death
- Approximately 90% patients with active disease have a positive c ANCA
- Diagnosis : biopsy of the involved tissues; pulmonary tissue offers the highest diagnostic yield, almost invariably revealing granulomatous vasculitis. Presence of c ANCA should be adjunctive & not replace tissue diagnosis.
- Treatment : the most effective therapy in this disease is cyclophosphamide 2 mg/ kg per day orally together with glucocorticoids for 1 year. The dose of cyclolphosphamide should be adjusted to maintain TLC > 3000 / mm^3.

GIANT CELL ARTERITIS

- Cranial arteritis / temporal arteritis
- Age > 50 years female s> males
- Systemic vasculitis of medium and large sized arteries
- It characterically involves one or more branches of carotid artery, particularly the temporal artery
- Histopathologically, the disease is a panarteritis with inflammatory mononuclear cell infiltrates within the vessel wall with frequent giant cell formation
- Clinically characterized by the complex of fever, anemia, raised ESR, headaches
- Polymyalgia rheumatic is closely associated & is characterized by stiffness, aching, and pain in the muscles of the neck, shoulders, lower back, hips, and thighs
- Tender, nodular temporal artery especially with repeated attacks
- Most feared complication : blindness due to ischemic optic neuropathy
- Aortic aneurysm is a late complication
- Diagnosis : biopsy of temporal artery
- Treatment : prednisone 40 to 60 mg/ d for approximately 1 month, followed by gradual tapering

HENOCH SCHONLEIN PURPURA

- 4-7 years
- M:F = 1.5 : 1
- Spring season
- Pathology
    - Small vessel vasculitis
    - Immune complex deposition
    - IgA in 50%
- Clinical features
    - Preceded by URI
    - MC presenting symptom in adults : palpable purpura (lower extremities, buttocks)
    - Platelet count is normal
    - Arthralgias
        - Renal involvement : mild GN, spontaneous resolution is the usual outcome; more severe in adults
        - GI involvement commoner in children; blood in stools
- Diagnosis : skin biopsy specimen shows leukocytoclastic vasculitis with IgA and C3 deposition by immunofluorescence
- Treatment :

  Prednisolone – useful for arthralgias, abdominal complications

  Not useful for GN / skin inv

- Patients rarely die; if they do : MC cause – renal failure

KAWASAKI DISEASE

Aka mucocutaneous lymphnode syndrome

- Children (80% < 4 years)
- Acute febrile illness with cervical LAP; erythema of lips, palms
- Desquamation of skin of fingers
- 80% cases benign & self limited
- 20% develop complications (in 3rd / 4th week) the heart bears the brunt of complicated disease
- MC: coronary artery aneurysm; also, pericarditis, myocarditis
- Cardiomegaly, MI
- Path : immunoregulatory defect with hyperfunction of T & B cells and macrophages
- Treatment is IVIG 2g/kg iv stat over 12 hours + aspirin 100mg/kg/d for 14 days (decreases complication rate)

TAKAYASU'S ARTERITIS

Aka pulseless disease / aortic arch syndrome / aorto-arteritis

- Panarteritis of medium and large arteries
- Intimal proliferation, fibrosis, vascularisation of media, narrowing of lumen

- Max inv of intima
- Strong predilection for aortic arch and its branches. Mc artery involved is subclavian
- Maximum involvement at origin of vessel
- Females < 40 years
- Constitutional symptoms +
- Elevated ESR, mild anemia, ↑ Ig
- Pain ± over involved vessels
- Absent pulses in involved arteries, discrepancy of BP between the 2 arms; arterial bruits
- MC cause of death : CHF > CVA
- Vessel involvement
- Subclavian > common carotid > abdominal aorta > renal > aortic arch
- Diagnosis : aortic arteriography
- Treatment

- Glucocorticoids
- Methotrexate (upto 25 mg/week)
- Angioplasty / other surgical repair only after inflammation has been brought under control by medication

SARCOIDOSIS

MC affected organ : LUNG

MC abnormality on CXR : hilar LAP > paratracheal LAP

MC site of skin lesions : FACE

MC neurological manifestation : unilateral VII nerve palsy

PATHOLGOY

Granulomas : core of mononuclear phagocytes; rim of CD4+ T cells langhans / foreign body giant cells; schaumann, asteroid & residual bodies

Clinical features of sarcoidosis

20-40 years

F>M

Nonsmokers (rare in smokers)

Constitutional features

60% insidious onset, 40% subacute onset

MED 5

Uveoparotid fever / heerfordt syndrome

Fever, parotid enl, anterior uveitis, VII nerve palsy

Lofgren syndrome

Erythema nodosum, bilateral hilar lymphadenopathy, arthritis

Peripheral lymphadenopathy is common, particularly involving the cervical, axillary, epitrochlear, and inguinal nodes. Palpation causes no pain & unlike in tuberculosis, the LN do not ulcerate

Lung – ILD

CXR : Type I : BHL

Type II : BHL + diffuse parenchymal changes

Type III : diffuse parenchymal changes

Erythema nodosum

B/L tender red nodules on anterior surface of legs

Histoplasma, EBV, IBD, OCP, penicillin, sulfonamides

MC eye lesion is anterior uveitis

MC endocrine involvement is hypothalamic – pituitary axis presenting mostly as diabetes insipidus

Parotid enlargement is a characteristic feature

Cardiac dysfunction due to left ventricular wall involvement can occur

Pregnancy

Pregnancy is unaffected

Disease improves during pregnancy

May flare immediate post-partum

Laboratory findings

Elevated serum ACE levels are seen in 2/3rd cases of sarcoidosis

Hypercalciuria

Kveim siltzbach test

Ga – 67 chest scan ; uptake in all areas of inflammation (especially LNs)

Treatment : prednisone 1 mg /kg daily for 4-6 weeks, followed by taper over 2-3 months

AMYLOIDOSIS

- Amyloidosis results from a sequence of changes in protein folding that leads to deposition of insoluble amyloid fibrils, mainly in the extracellular spaces of organs and tissues. All amyloid deposits contain the pentaxin serum amyloid protein and glycosaminoglycans

- AL: immunoglobulin light chains – primary / myeloma

- AA: reactive / secondary – MC type in India : MC cause is tuberculosis

- Aβ2m : β^2 – microglobulin – hemodialysis

- Aβ : alzheimer's disease / down syndrome

- ATTR: transthyretin – familial / senile systemic amyloidosis

AL

- Synthesized by plasma cells

- $\sim$ 20% of AL pts hae myeloma

- $\sim$ 20% of myeloma pts have amyloidosis

- λ: κ = 2:1

- Multiple myeloma - λ: κ = 1:2

- Nephropathy, cardiomyopathy, neuropathy, hepatomegaly

- Macroglossia, malabsorption

- Serum, urine immuneelectrophoresis, bone marrow biopsy for diagnosis

Treatment: 1. Cyclical oral melphalan with prednisone

2.High dose melphalan with stem cell rescue

3.Idodoxorubocin

MED 5

AA

-Serum amyloid A synthesis in liver

-MC due to TB; rheumatoid arthritis, osteomyelitis, leprosy are other causes

-IL-1, IL-6, and TNF stimulate hepatic synthesis of serum amyloid A

-Proteinuria, hepatosplenomegaly

-Diagnosis : elevated serum amyloid protein, positive immunohistochemical staining for AA protein in tissue specimen

-Treatment : 1. Treat underlying inflammatory condition

2.Colchicine for preventation & treatment of AA amyloidosis is FMF

Familial amyloidosis

- Family history of peripheral neuropathy, nephropathy plus any of the following
- Carpal tunnel syndrome
- Vitreous opacities
- Renal disease
- Autonomic nervous system symptoms
- Cardiovascular disease
- Gastrointestinal disease
- Sensorimotor dissociation

-Diagnosis : protein variant in serum, DNA-based test for mutant gene

-Treatment : liver transplantation

Sago spleen : amyloid in splenic follicles

Lardaceous spleen : amyloid in red pulp

1st sign of systemic amyloidosis: proteinuria

Usual kidney inv: nephritic syndrome

Biopsy : abdominal fat, rectum, skin, gingival

Congo-red stain : pink – red with light microscopy

-Green birefringence with polarizing microscope

MED 5

INFLAAMATORY MYOPATHIES

Polymyositis, dermatomyositis, inclusion body myositis

Anti-Jo1/ anti-histidyl tRNA synthetase antibodies

	PM	DM	IBM
Age/sex	Adults F>M	Adults & children F > M	> 50 years M > F
Clinical features	Progressive symmetric weakness		
Clinical features	Proximal muscle involvement early Distal – late (if at all)	Both proximal & distal early; distal often earlier	
Clinical features	Ocular muscles spared Sensation, DTRs normal		
Clinical features	Facial muscles spared	Mild facial weakness	
Clinical features	With advanced / untreated disease – wasting & respiratory muscle invovlment		
Associations A.CTDs	MCTD, SLE, RA, SSc, sjogren's	SSc, MCTD	Same as PM
B. Systemic autoimmune Ds	Crohn's ds, PBC, celiac ds, MG etc		
C. Malignancy		+ (ovary, breast, melanoma, colon, NHL)	

Pathogenesis:

- PM & IBM : T-cell mediated muscle injury
- DM : humoral immunity mediated

DM

- Heliotrope rash : blue – purple discoloration on upper eyelids with edema

- Gottron's rash : erythema of knuckles with raised eruptions
- V sign / shawl sign : depending on distrubiton of rash on shoulders / trunk
- Mechanics hands : thick palms with cracked fingers
- DM sine myositis : rash without muscle weakness

IBM

Early distal muscle weakness : especially foot extensors and deep finger flexors (flexor pollicis longus)

ILD : 10-20%; assoc with anti-jo 1 antiodies

Diagnosis

CK

↑ in 75% with PM

↑ / normal in DM / IBM

Aldolase : ↑ in 90% with PM

Definitive diagnosis

Muscle biopsy

PM : CD8+ / MHC I complexes; no vacuoles

DM: perivascular (endomysial) inflammation; perfiascicular atrophy

IBM : CD 8+ / MHC I complexes, vacuolated muscle fibres

Treatment

Glucocorticodis prednisone – 1mg/kg/day for 3-4 weeks, then taper gradually

Azathioprine (up to 3 mg/kg/day) or methotrexate : (7.5 mg/week gradually increasing to 25 mg/week)

Intravenous immunoglobulin (2g/kg divided over 2-5 days)

Cyclosporine, chlorambucil, cyclophosphamide, or mycophenolate mofetil may be used

NEUROLOGY SET - 1

1.Which channel type is involved in Familial hemiplegic migraine?
- a) Sodium
- b) Calcium
- c) Both
- d) None

2.Which of the following is not a contraindication for MRI?
- a) Cochlear prostheses
- b) Bone growth stimulators
- c) Swan ganz catheter
- d) Cardiac pacemaker
- e) None of these

3.Increased ICT is associated with all except
- a) Paraparesis
- b) Abducent paralysis
- c) Head ache
- d) Visual blurring

4.Most common site of hypertensive bleeds
- a) Pons
- b) Thalamus
- c) Putamen
- d) Sub cortical white matter

5.Most common cause of sub arachnoid bleed
- a) Hypertension
- b) Berry aneurysm
- c) AV malformation
- d) Tumors

6.Sub dural hematoma most commonly results from
- a) Rupture of intra cranial aneurysm
- b) Rupture of cerebral AVM
- c) Injury to cortical bridging veins
- d) Hemophilia

7.A45 year old hypertensive presents with sudden abnormal flinging movements in right upper and lower limb. Most likely site of hemorrhage
- a) Pons
- b) Substantia nigra
- c) Caudate nucleus
- d) Sub thalamic nuclei

8.Most common cause of delayed neurological deterioration in a case of CVA at one week is
- a) Re bleed
- b) Vaso spasm
- c) Embolism
- d) Hydrocephalus

9.Lacunar infarcts manifests as
- a) Pure sensory weakness
- b) Pure motor weakness
- c) Ataxic hemi paresis
- d) Any of these

10.A medial temporal lesion produce
a) Visual amnesia
b) Auditory amnesia
c) Apraxia
d) Anterograde learning problems

11.A lesion in inferior frontal gyrus causes
a) Defect in articulation
b) Defect in comprehension of written language
c) Defect in comprehension of spoken language
d) Motor aphasia

12.Pontine stroke is associated with all except
a) Bilateral pin point pupil
b) Pyrexia
c) Vagal palsy
d) Quadriparesis

13.Single most common finding in aphasic patients
a) Anomia
b) Apraxia
c) Alexia
d) Agraphia

14.When wernicke area is affected it will result in

	Comprihension	Repetition	Fluency
a)	Impaired	Impaired	Preserved
b)	Preserved	impaired	Impaired
c)	Impaired	Impaired	impaired
d)	Preserve	Impaired	Preserved

15.Ipsilateral 3rd CN palsy with contra lateral hemiplegia
a) Millard gubler syndrome
b) Weber syndrome
c) Foville syndrome
d) Benedict syndrome

16.Millard gubler includes all except
(a) Vth CN
(b) VIth CN
(c) VIIth CN
(d) Contra lateral hemiparesis

17.Wallenberg syndrome is caused by thrombosis of
a) AICA
b) PICA
c) Vertebral artery
d) Basilar artery

18.Lateral medullary syndrome features all except
a) Ipsilateral numbness of face
b) Horner's syndrome
c) Ipsilateral ataxia
d) Contra lateral paralysis

19.Most common cause of stroke among OCP using females
a) CVT
b) Moyamoya D
c) Atherosclerosis
d) Hypertension

20.Golden hour of thrombolysis in stroke
a) 3
b) 6
c) 12
d) 24

21.Prophylaxis of migraine
a) Sumatriptan
b) amitriptyline
c) Nifedipine
d) Diazepam

22.Absence seizures are characterized on EEG by
a) 3Hz spike and wave
b) Generalized poly spikes
c) Hypsarrhythmia
d) None of these

23.True about juvenile Myoclonic epilepsy are all except
a) Focal seizure
b) Myoclonus
c) Respond to Valproate
d) Spike and wave in EEG

24.Myoclonic seizures are seen in
a) SSPE
b) SLE
c) Herpes encephalitis
d) Strychnine poisoning

25.Well recognized side effects of prolonged phenytoin use includes all except
a) Hirsutism
b) Lymphadenopathy
c) Ataxia
d) Hypoglycemia

26.All the following drugs are used in the treatment of status epilepticus except
a) Phenytoin
b) Diazepam
c) Thiopentone sodium
d) Carbamazepine

27.EEG with spike and dome is characteristic of
a) Grand mal
b) Petit mal
c) Temporal lobe epilepsy
d) None

28.DOC for absence seizure
a) Valproate

b) Lamotrigine
c) Gabapentin
d) Carbamazepine

29.Renal stones are produced by
a) Levitracitam
b) Felbamate
c) Zonisamide
d) Tiagabin

30.Select incorrect statement
a) Acetazolamide usefull in catamenial epilepsy
b) Seizure frequency during pregnancy will remain unchanged in ~50% of women, increase in 30%, and decrease in 20%
c) Enzyme-inducing drugs such as phenytoin, phenobarbital, and primidone cause a transient and reversible deficiency of vitamin K–dependent clotting factors in ~50% of newborn infants.
d) it is currently recommended that pregnant women be maintained on effective drug therapy
e) none of these

31.All the following are known predisposing features of Alzheimer's disease except
a) Down's syndrome
b) Low education level
c) Smoking
d) Female sex

32.True about etio pathogenesis of Alzheimer's disease are all except
a) Absence of tau protein
b) Involvement of apolipoprotein E
c) Presenilin 1&2 involvement
d) Mutation in chr 21

33.Lesion in Alzheimer's disease is commonest at
a) Amygdale
b) Nucleus of maynert
c) Pineal gland
d) Prefrontal sulcus

34.Which of the following drugs used in treatment of alzhemeres disease acts by blocking NMDA channel
(a) Donepazil
(b) Rivastigmine
(c) Memantine
(d) Glantamine

35.Dementia with lewy body is associated with
a) Aβ
b) Tau
c) α synuclein
d) PrP protein

36.Cap grass syndrome may be the presenting complaint of
a) AD
b) Fronto temporal dementia
c) Lewy body dementia
d) Vascular dementia

37.Treatable dementia is

a) SACD
b) Picks D
c) CJD
d) AD

38.Huntington's d is due to
a) Nigro striatal dopaminergic neuron
b) Intra striatal cholinergic neuron
c) Intra striatal cholinergic and GABAnergic neuron
d) Intra striatal GABAnergic neuron

39.True about CJD
a) Corneal implants can transmit disease
b) Caused by RNA virus
c) Caused by DNA virus
d) Arthropod born

40.NPH is characterized by all except
a) Aphasia
b) Dementia
c) Ataxia
d) Urinary incontinence

41.All are features of Wernicke's encephalopathy except
a) Cogwheel rigidity
b) Opthalmoplegia
c) Ataxia
d) Alteration in mental state

42.All the following are features of pseudo tumor cerebri except
a) Increased ICT
b) Convulsions
c) Papilledema
d) Normal CT

43.Extra pyramidal symptoms are not a feature of
a) Carbon monoxide poisoning
b) Paralysis agitans
c) CVA
d) MS

44.Which of the following is not seen in parkinsonism
a) Preserved postural reflex
b) Hypo kinesia
c) Rigidity
d) Static tremor

45.Drug which can produce parkinsonism
a) Bromocriptine
b) Amantadine
c) Phenothiazine
d) Atropine

NEUROLOGY SET - 2

1.Degenerative changes in Huntington's chorea is seen in
a. Cerebellum

b. Caudate nucleus
c. Sub thalamic nucleus
d. Red nucleus

2.Slow, distal, writhing, involuntary movements with a propensity to affect the arms and hands is a feature of
a. Athetosis
b. Chorea
c. Tics
d. Myoclonus

3.True about essential tremor are all except
a. Most common involuntary movement
b. High frequency tremor up to 11 Hz
c. Bilateral and symmetrical
d. Characteristically worsens with alcohol
e. Cerebellum and inferior olive are implicated as tremor pacemakers

4.True about Huntington's chorea is all except
a. Autosomal dominant
b. Strikes striatum
c. Increased number of CAG repeats
d. Genetic screening of all family members should be done

5.True statement regarding Myoclonus include
a. Sudden, brief (<100 ms), shock like, arrhythmic muscle twitches.
b. It can be focal, multi focal, segmental, or generalized.
c. Asterixis is a negative Myoclonus
d. Differs from tics in that they are suppressible

6.Which of the following can produce a chronic progressive symmetric cerebellar ataxia?
a. Post viral
b. Hypothyroidism
c. Multiple sclerosis
d. Dandy walker deformity

7.Which of the following is not an Autosomal dominant trait?
a. Friedreich's ataxia
b. Spino cerebellar ataxia
c. Episodic ataxia
d. DRPLA

8.Mutation in the gene for α_{1A} voltage-dependent calcium channel subunit (*CACNA1A* gene) at 19p13 result in
a. SCA 6
b. Familial hemiplegic migraine
c. Episodic ataxia
d. All of these

9.True about Friedreich's ataxia are all except
a. Most common inherited ataxia
b. Present by 60 years
c. Extensor plantar with absent ankle jerk
d. Cardiac involvement in 90 %
e. Idebenone is a new drug used in treatment

10.Which of the following infections causes acute sporadic motor neuron disease?
a. Polio

b. Herpes zoster
c. Coxsackie virus
d. All of these

11.All the following statements regarding ALS are true except
a. Most common form of progressive MND
b. Involve both UMN and LMN
c. Familial form is Autosomal dominant and is due mutation in SOD1
d. Ocular motility involved early
e. Fasciculation is characteristic

12.Which of the following is used in the treatment of ALS?
a. RILUZOLE
b. Ceftriaxone
c. IGF 1
d. Anti sense oligonucleotides (ASO)
e. All of these

13.Which SMA presents with predominant proximal weakness?
a. Werdnig-Hoffmann disease
b. Chronic childhood SMA
c. Kugelberg – wilander disease
d. None of these

14.Which of the following is not a sympathetic function?
a. Orgasm
b. Erection
c. Ejaculation
d. Sweating

15.Acetyl choline is the neurotransmitter for all except
a. Sympathetic pre ganglionic
b. Sympathetic post ganglionic
c. Parasympathetic pre ganglionic
d. Parasympathetic post ganglionic

16.Following statements about tic doloureux are true except
a. Excruciating paroxysms of pain in the distribution of the fifth cranial nerve
b. Ophthalmic division most commonly involved
c. Trigger zones
d. No objective signs of sensory loss

17.Bilateral facial palsy is seen in
a. Lyme's disease
b. Ramsay hunt syndrome
c. Guillain-Barré syndrome
d. Melkerson Rosenthal syndrome
e. All of these

18.T4 spinal cord level corresponds to which vertebral level
a. T2
b. T3
c. T4
d. T5

19.Which is not a feature of central spinal cord syndrome?
a. Dissociated sensory loss

b. Suspended sensory loss
c. Loss of pain and temperature on opposite side below the lesion
d. syringomyelia classic example

20.Which is not a feature of extra medullary lesion?
a. Prominent radicular pain
b. Spasticity of leg
c. Late bladder involvement
d. Sacral sparing

21.Incorrect statement regarding neoplastic spinal cord compression
a. Thoracic cord most commonly involved
b. Batson's plexus responsible for sacral and lumbar metastasis of prostatic cancer
c. Nocturnal pain
d. Involvement of disc space and spread to adjacent vertebra characteristic

22.Incorrect statement regarding spinal cord vascularity
a. A pair of anterior spinal A supply the anterior 2/3 of spinal cord
b. A pair of post spinal A supply the post 1/3
c. Ant spinal A is fed by artery of Adamkeiwicz at T11-L2
d. T3-T4 and boundary between ant 2/3 and posterior 1/3 lies in watershed zone and are at the greatest risk of ischemia

23.Which of the following is not a feature of syringomyelia
a. Painless burns in hand
b. 50% association with chiari type 1 malformation
c. Balaclave helmet type of sensory loss
d. Central cord syndrome
e. None of these

24.Not a feature of SACD
a. Extensor plantar
b. Absent ankle jerk
c. Positive Romberg
d. Myopathy
e. Optic atrophy

25.Select the incorrect statement regarding tabes dorsalis
a. Exaggerated reflexes
b. Acute abdominal pain with vomiting
c. Positive Romberg
d. Bladder incontinence
e. ARP

26.Incorrect statement regarding multiple sclerosis
a. Demyelinating disorders are characterized by inflammation and selective destruction of central nervous system (CNS) myelin
b. More common in males
c. Sensory loss most common initial presentation
d. Four clinical types

27.Most common primary intracranial neoplasm
a. Astrocytoma
b. Oligodendroglioma
c. Ependymoma
d. Medulloblastoma

28.True statement regarding astrocytoma
a. Pilocytic astrocytoma is the most common childhood brain tumor
b. Glioblastoma multiforme is most aggressive astrocytoma
c. High grade metastasize to spinal cord via CSF
d. Temozolamide is an orally active alkylating agent against glioma
e. All of these

29.Incorrect statement regarding ependymoma
a. Most common site is filum terminale of spinal cord
b. Myxopapillary histology
c. In children occurs within ventricle, commonly 4^{th} ventricle
d. Drop metastasis
e. None of these

30.True statement regarding medulloblastoma
a. Most common malignant brain tumor of children
b. Arise from neural precursor cells and occurs in posterior cranial fossa
c. PNET is histologically similar but occurring in adults or supra tentorially in children
d. Radiosensitive
e. All of these

31.Incorrect statement regarding CNS lymphoma
a. High grade B cell lymphoma
b. More common in immuno compramised
c. Associated with Ebstein bar virus
d. Secondary CNS lymphoma most commonly occur in lepto meninges
e. None of these

32.True regarding meningioma
a. Mesodermal origin
b. Benign extra axial tumor attached to dura
c. Dural tail
d. All of these

33.Schwannoma most commonly arise from
a. Vestibular division of 8CN
b. Cochlear division of 8CN
c. 7CN
d. 5CN

34.Incorrect statement regarding craniopharyngeoma
a. Remnant of Rathke's pouch
b. Supra sellar
c. Calcification common
d. Drop metastasis

35.Characteristic feature of frontal lobe tumor
a. Abnormal gait
b. Aphasia
c. Distractibility
d. Anti social behavior

36.Triad of tuberous sclerosis is all except
a. Epilepsy
b. Adenoma sebacium

c. Low intelligence
d. Hydrocephalus

37.About VHL which is not true
a. Cerebellar hemangioblastoma
b. Pheocromocytoma
c. RCC
d. Ca stomach

38.CSF picture with protein and sugar increased and neutrophils is suggestive of
a. Tuberculous meningitis
b. Viral
c. Bacterial
d. Partially treated meningitis

39.Commonest cause of sporadic encephalitis
a. Japanese B virus
b. Herpes simplex
c. HIV
d. Rubeola virus

40.DOC for cryptococcal meningitis
a. Pentostatin
b. Amphotercin B
c. Clotrimazole
d. Zidovudine

41.Incorrect statement regarding neurocysticercosis
a. Most common CNS parasitic infection
b. Seizure most common presenting complaint
c. Brain parenchyma most common location
d. DOC is praziquental

42.All are true regarding CNS infection except
a. Measles virus is causative agent for SSPE
b. MRI in CMV shows bilateral fronto temporal hyper intense lesion
c. Prions causes spongiform encephalitis
d. JC virus is the causative agent for multi focal leuco encephalopathy

43.In prion disease all the following are true except
a. Caused by infectious protein
b. Biopsy of brain diagnostic
c. Neurodegenerative disease
d. Myoclonus found only in 10%

44.Most common prion disease in human
a. Scrapie
b. Kuru
c. CJD
d. FFI

45.All are true about GBS except
a. Predominant motor involvement
b. Early bladder involvement
c. Albumin cytological dissociation
d. Areflexia

46.GQ1b antibodies are associated with
a. AIDP
b. AMAN
c. MFS
d. CIDP

47.Not a feature of polyneuropathy
a. Fairly symmetric
b. Distal glove and stocking
c. Rapid onset weakness and atrophy
d. Sensorimotor

48.All produce small fiber sensory neuropathy except
a. Sjogrens syndrome
b. Leprosy
c. Amylodosis
d. Anti retro viral drugs

49.All are motor predominant neuropathy except
a. Porphyria
b. Pyridoxine toxicity
c. Diphtheria
d. Lead poisoning

50.All are features of axonal neuropathy except
a. Distal weakness
b. Pain and temperature more than vibration and touch
c. Nerve conduction velocity affected more than amplitude
d. Slow recovery

51.Neuropathy associated with HIV
a. Distal symmetrical polyneuropathy
b. CIDP
c. Mononeuritis multiplex
d. All of these

52.All causes ascending paralysis except
a. DM
b. Diphtheria
c. GBS
d. Porphyria

53.All are features of myasthenia except
a. Absent DTR
b. Proximal muscle weakness
c. Fatigability
d. Ocular involvement

54.Incorrect statement regarding myasthenia
a. Common in females
b. Thymus abnormal in75%
c. Anti Ach receptor antibody seen in 85%
d. Thymectomy should be done in all patients with generalized MG
e. Patients with anti MuSK antibodies respond best to thymectomy

55.Lambert Eaton is differentiated from myasthenia by

a. Pre synaptic disorder
b. Distal weakness
c. Antibody directed against p/q calcium channel
d. Areflexia and autonomic symptoms
e. Absence of fatigability

56.Incorrect statement regarding Duchenne muscular dystrophy
a. X linked recessive
b. Deletion in dystrophin gene that encodes a sarcolemmal protein
c. Mental impairment
d. Cardiomyopathy
e. None of these

57.Incorrect statement regarding myotonic dystrophy
a. Autosomal dominant
b. CTG tri nucleotide repeats on chromosome 19
c. Distal weakness
d. Serum CK markedly elevated
e. Hatchet facies

58.All are congenital myopathy except
a. Wilander myopathy
b. Central core myopathy
c. Nemaline rod myopathy
d. Centro nuclear myopathy

59.Not a feature of dermatomyositis
a. Heliotrope rash
b. Gottron's papules
c. Shawl sign
d. Mechanics hand
e. None of these

60.Incorrect statement regarding polymyositis
a. Ocular muscle involvement
b. Progressive symmetric proximal muscle weakness affecting adults
c. Associated with collagen vascular disease, infection and drugs
d. Diagnosis of exclusion

61.Incorrect statement regarding Inclusion body myositis
a. Most common inflammatory myopathy
b. Symmetric proximal weakness
c. In patient > 50yrs
d. Associated with autoimmune disease

HEMATOLOGICAL MALIGNANCIES

1.All the following chromosomal disorders are associated with increased incidence of AML EXCEPT.
a) Down syndrome
b) Klinefelters syndrome
c) Patau syndrome
d) None of these

2.Flowcytometry analysis of an AML patient showed CD41 and CD61 positivity it belongs to FAB classification
a) M0
b) M3

c) M6
d) M7

3. Granulocytic sarcomas are associated with which cytogenitic abnormality
a) t (8;21)
b) t (15;174)
c) inv (16
d) del (5q)

4. The following statements about AML are true **EXCEPT.**
a) Fatigue is most common presenting complaint
b) Gingival hyperplasia and leukemia cutis is characteristic of monocytic subtype
c) There is both decrease in platelet function and number.
d) It causes normocytic normochromic anemia
e) None of these

5.All are bad prognostic indicators of AML EXCEPT.
a) Age more than 60yrs
b) TLC > 100000 /micro liter
c) Secondary leukemias
d) Presence of t (8;21)

6.In a patient with acute leukemia immunophenotype pattern CD19, CD10, CD33 & CD13 positive he may probably have
a) Biphenotypic
b) ALL
c) AML M2
d) AML M0

7.The following statements above the treatment of AML are true EXCEPT.
a) The most commonly used CR inducing regimen is 7 & 3 regimen using cytarabine and anthracycline
b) Tretinoin + anthracycline is the safest and most effective treatment for APL
c) Once relapse has occurred AML is generally curable only by SCT
d) Autologous SCT has a lower toxicity and lower relapse rate compared to allogenic SCT

8.Anti body targeted chemotherapy used in treatment of AML
(a) Gemtuzumab ozogamicin
b) Denileukin diftitox
c) Ibritumomab Tiuxetan
(d) Tositumumab

9.60 yr old man presents with fatigue wt loss and heaviness in left hypochondrium for 6 months. The hemogram showed Hb 10gm /dl. TLC 500000 /mm.q platelet 4lakh, basophlis 6%, metamyelocyte 1%, myelocyte 18%, promyelocyte 2%, and blast 3%. The most likely cytogenetic abnormality in this case.
a) t (1;21)
b) t (9;22
c) t (15;17)
d) trisomy 21

10.Which one of the following is not a criteria for making a diagnosis of CML in accelerated phase
a) Blast 10-19 % of WBC in peripheral blood
b) Basophils 20% of WBC in peripheral blood
(c) Increased spleen size unresponsive to therapy
d) Persistent thrombocytosis

11.Which of the following is not a prognostic indicated according to SOKAL index in CML

a) Percentage of circulating blasts
b) Platelet count
c) Percentage of eosinophils and basophils
d) Cytogenetic clonal evaluation

12.DOC for treatment of CML
a) Imatinib mesylate
b) Interferon alpha
c) Hydroxurea
d) Homoherringtonine

13.Labortary evaluation for DD of chronic myeloproliferative disorders include all the following EXCEPT.
a) Chromosomal evaluation
b) Bone marrow aspiration
c) Flowcytometric analysis
d) Determination of RBC mass

14.Which one of the following is not compactable with diagnosis of juvenile myelo monocytic leukemia
a) Peripheral blood monocytosis more than $1X10^9$ /L
b) Increased HbF level for age
c) Presence of abl-bcr fusion gene
d) GM –CSF hypersensitivity of myeloid progenitor's invitro

15.Lymphoplasmacytic lymphoma is associated with infection with
a) HIV
b) HTLV-1
c) Hepatitis C virus
d) HHV-8

16.Poor prognostic indicator of ALL is
a) Female sex
b) Leukocyte count < 50000
c) Age>1yr
d) Hypodiploidy

17.Which of following FAB subtypes of ALL has best prognosis
a) L1
b) L2
c) L3
d) None of these

18.All the following statements regarding treatment of ALL are true EXCEPT.
a) Steroids used for induction
b) Bone marrow transplantation is the treatment of choice
c) Prophylactic intrathecal chemotherapy using methotrexate is critical part of ALL treatment
d) Tumor lysis syndromes may complicate treatment of ALL

19.48yr old woman admitted with history of weakness of 2months on examination cervical lymphnodes where found enlarged and spleen was palpable 2cm below the costal margin.Her Hb was 10.5 g/dl platelet count $237X10^9$/L and TLC $40X10^9$ which include 80% mature lymphoid cells with coarse clumbed chromatin bonemarrow revealed a nodular lymphoid infiltrate.The peripheral blood lymphoid cells where positive for CD19, CD5, CD20 & CD23 negative for CD79B & FMC-7. Which of the following statements is not true about this disease.

a) Trisomy 12 correlates an aggressive clinical course
b) Abnormalities of 13q14 associated with long term survival
c) Cases with 11q deletions have excessive lymphadenopathy
d) t (11;14) is present in most of the cases

20.CLL is differentiated form mantle cell lymphoma by
a) CD5
b) CD19
c) CD20
d) CD23

21.A CLL patients presenting with thrombocytopenia belong to
a) Rai stage 0 Binet A
b) Rai 1 Binet A
c) Rai 4 Binet C
d) Rai 2 Binet B

22.Drug of choice for young patient presenting with CLL
a) Chlorambucil
b) fluderabine
c) Rituximab
d) Alemtuzimab

23.Which of the following cells seen in hodgkins D is hetrogenetically different from the rest.
a) R-S cells
b) Mononuclear variant
c) Lacunar cells
d) Popkorn cells

24.Regarding clinical features of hodgkins D the following statements are true EXCEPT.
(a) Cervical and supraclavicular nodes are most commonly involved
(b) Pel-epstein fever is characteristically described in it
(c) Pain in lymphnodes on alcohol ingestion is seen
(d) Paraneoplastic syndromes include nephrotic syndrome and cerebellar degeneration
(e) None of these

25.Hodgkins D associated with best prognosis
a) Nodular sclerosis
b) Mixed cellularity
c) Lymphocyte predominant
d) Lymphocyte depletion

26.Following statements about hodgkins lymphoma are true EXCEPT.
a) Localized to single axial group of nodes
b) Orderly spread by contiguity
c) Mesentric nodes and waldeyar ring commonly involved
d) Extra nodal involvement uncommon

27.Which of the following is noninvasive staging of hodgkins lymphoma
a) An Arbor staging
b) Costwalds staging
c) Both

d) None

28.All are T-cell lymphoma EXCEPT.
a) Mycosis fungoides
b) Mantle cell lymphoma
c) Angioimmunoblastic lymphoma
d) Anaplastic large cell lymphoma

29.All the following statements about hairy cell leukemia are true EXCEPT.
(a) Typically presents with pancytopenia and splenomegaly
b) TRAP positivity typically seen
c) Prone to unusual infections like mycobacterium avium intercellulare
d) dismal prognosis and treatment is palliative

30.Prefered treatment for hairy cell leukemia
a) Interferon alpha
b) Cladrabine
c) Pentostatin
d) Chlorambucil

31.The following statements about extra nodal marginal zone lymphoma of MALT type are true EXCEPT.
a) Characteristic pattern of infiltration of small lymphocytes that are monoclonal B-cells and CD-5 negative
b) Most common site is stomach
c) 95% of gastric MALTomas are associated with H.pylori infection and those that are not usually express t (11;18)
d) Surgery has only palliative role.

32.lymphomatosis polyposis in large intestine is associated with
a) Follicular lymphoma
b) Mantle cell lymphoma
c) MALToma
d) Diffuse large B-cell lymphoma

33.The following statements about follicular lymphoma are correct EXCEPT.
a) B-Cell phenotype with t(14;18) and BCL – 2 over expression
b) Most common presentation is with new painless lymphadenpathy
c) Histologic transformation to aggressive lymphomas are rare
d) They can under go spontaneous regression

34.Most common type NHL
a) Follicular lymphoma
b) Mantle cell lymphoma
c) MALToma
d) Diffuse large B-cell lymphoma

35. Following statements about burkitts lymphoma are true EXCEPT.
a) 30%^ of childhood nonhodgkins lymphoma
b) Diagnosed by demonstration of high proliferation fraction and presence of t (14;18)
c) Prophylactic therapy to CNS mandatory
d) It is curable by chemotherapy

36.Flower cells in peripheral blood seen in
a) Adult T-cell leukemia
b) Sezary syndrome
c) Burkitts leukemia
d) Diffuse large B-cell lymphoma

37. Regarding Mycosis fungoides select the true statements
a) It is cutaneous T-cell lymphoma
b) Sezary syndrome is characterized by erythroderma and circulating tumor cells
c) Often presents as eczema and progress as patch,plaque to tumor state
d) Treatment is rarely curable often palliative
e) All of these

38. Intermediate form of NHL are all EXCEPT.
a) Diffuse small cell cleaved
b) diffuse large cell
c) Mycosis fungoides
d) Diffuse mixed

39.which of the following is not a major criteria for diagnosis of multiple myeloma
a) Lytic bone lesion
b) Plasmacytoma on tissue biopsy
c) Bone marrow plasma cytosis >30%
d) M spike >3gm% for IgG and >2gm% for IgA

40.Single most powerful predictor for survival in multiple myeloma
a) M component
b) S.calcium
c) β 2 microglobulin
d) S.Creatinine

41.Most common cause of renal failure in multiple myeloma
a) glomerular deposit of amyloid
b) Hyper urecemia
c) Hyper calcemia
d) Recurrent infections

42.An 80 yr old asymptomatic woman was detected to have a monoclonal spike on serum electrophoresas (IgG level 1.5gm /dl) bone marrow revealed plasma cells of 8% most likely diagnosis.
a) Multiple myeloma
b) Metastasis
c) Monoclonal gammopathy of unknown significance
d) Walden storms macro globulinemia

43.All used in treatment of Walden storms macro globulinemia EXCEPT.
a) Plasma pheresis
b) Cladribine
c) Rituximab
d) Doxorubicin

44. Rituximab is useful in all except
a) NHL
b) RA
c) PNH
d) SLE

45. Most common lymphoma in spleen
a) Small lymphocytic lymphoma
b) Burkitts lymphoma
c) Anaplastic large B cell lymphoma

d) Adult t cell leukemia

46. A patient investigated for anemia has a dry marrow tap peripheral smear reveal tear drops cells likely diagnosis is
a) Leukemia
b) Lymphoma
c) Myelofibrosis
d) Polycythemia

47. Which is not a component of 'POEMS' syndrome
a) Poly neuropathy
b) Organomegaly
c) Encephalopathy
d) Multiple myeloma
e) Skin changes

48. Select incorrect statement
a) IgD myeloma may present with no evidence of M-spike on serum electrophoresis
b) Diagnosis of plasma cell leukemia can be made if circulating peripheral blood plasmoblast comprises >10% white cells
c) The smoldering myeloma plasma cell constitute 10 to 30% of total marrow cellularity
d) In patients multiple myeloma monoclonal light chain can be detected in both serum and urine

49. Most common heavy chain disease
a) Alpha heavy chain disease (Seligmanns disease)
b) Gama heavy chain disease (Franklin's disease)
c) Mu heavy chain disease
d) None of these

50. Antigenic determinants that are unique to the immunoglobulins produced by a given clone of antibody-producing cells.
a) Isotype
b) Idiotype
c) Allotype
d) xenotype

HEMATOLOGY PART -II

1. The following statement about ABO blood group system are true EXCEPT
a) It was the first blood group antigen system, recognized in 1900
b) These antigens are carbohydrates attach to a precursor backbone made of glycosphingolipids or glycoprotein
c) Genes that determine A&B phenotype are found on chromosome1 and expressed as Mendelial co-dominant manner
d) Bombay phenotype are rare individuals who lack H gene

2. Which of the following blood system have carbohydrate antigen?
a) Rh
b) Lewis
c) Kell
d) Duffy

3. Ideal component for transfusion in a patient who have sustained acute hemorrhage of >25% of total blood volume loss.
a) Whole blood
b) PRBC
c) FFP
d) Platelet concentrates

4. Following statements about blood components are true EXCEPT.
a) Whole blood stored at 4^0C to maintain erythrocyte viability
b) 1 unit of PRP increase platelet count by 5000 to 10000 /microL
c) FFP is an a cellular component and does not transmit intracellular infections like CMV
d) Cryoprecipitate is ideal for supplying fibrinogen to volume sensitive patient
e) None of these

5. The most frequent reaction associated with transfusion of cellular blood component
a) FNHTR
b) TRALI
c) GVHD
d) Anaphylaxis

6. The following statements about non immunological reaction of blood transfusion are true EXCEPT.
a) Transfusion of refrigerated blood can cause cardiac arrhythmias
b) Citrate used for anticoagulation can cause hypocalcaemia
c) Transient hypotension may be noted in patients taking ACE inhibitors
d) PRBC and FFP are contaminated by bacteria since they are stored at 1-6^{o}C

7. The following statements about hematopoetic stem cell transplant are true EXCEPT.
a) Bone marrow aspirated from anterior and posterior iliac crest has traditionally been the source of stem cell transplantation
b) Use of peripheral blood stem cell result in less rapid hematopoetic recovery compared to marrow transplant
c) Use of cord blood as a source of stem cell results in slower engraftment and lower incidents of GVHD
d) None of these

8. The following statements about GVHD are true EXCEPT.
a) Result of allogenic T-cells that are either transferred with donor's stem cells or develops from it reacting with antigenic target on host cell
b) GVHD developing with in first 3 months post transplant is termed as acute GVHD
c) Combination of methotrexate an cyclosporine used widely for prevention of GVHD
d) Patients with chronic GVHD should receive cotrimoxazole prophylaxis as they are susceptible to infections

e) None of these

9. Thrombocytopenia occurs in all EXCEPT.
a) HSP
b) TTP
c) DIC
d) Wiskott Aldrich syndrome

10. Platelet transfusion is not indicated in
a) Dilutional thrombocytopenia
b) Immunological thrombocytopenia
c) Aplastic anemia
d) DIC

11. All are true about chronic ITP EXCEPT.
a) Most common woman aged 20-40 years
b) Autoimmune disorder with antibody directed against Gp IIb/IIIa and less frequently against Gp Ib/IX complex
c) Diagnosis is clinical and bone marrow rarely required
d) Specific therapy not required unless platelet count <20000 our there is extensive bleeding

12. Most common inherited bleeding disorder
a) Factor VIII deficiency
b) Factor IX deficiency
c) von Willebrands disease
d) Factor X deficiency

13. Select the incorrect statement about vWD
a) vWF synthesized by endothelial cells and megakaryocyte
b) All types of vWD are inherited as autosomal dominant traits
c) Desmopressin very useful in the treatment of Type- I vWD
d) Waldenstorms macro globulinemia and wilms tumor associated with acquired vWD

14. All are true about Bernad soulier syndrome EXCEPT.
a) Defect in Gp IIb/IIIa complex
b) Mild thrombocytopenia
c) Large lymphocytoid platelet
d) None of these

15. All are seen in TTP EXCEPT.
a) Fever
b) Hemolysis
c) Hypertension
d) Low platelet count

16. Which of the following differentiate HUS from TTP
a) HUS is disease of infancy and early childhood and associated with infection with E coli and shigella
b) Disorder remains localized to Kidney, where hyaline thrombi are seen in afferent arterioles and glomerullar capillaries
c) Neurological feature other than those associated with uremia not see
d) All of these

17. True about hemophilia are all EXCEPT.
a) PTT increased
b) PT increased

c) CT increased
d) Serum factor VIII decreased

18. All true regarding symptomatology of hemophilia EXCEPT.
a) Symptomatics usually have factor VIII <5%
b) Excessive cephalhematoma or excessive bleeding during cirucumcision are first symptom of cevere disease
c) Femoral neuropathy and pseudo tumor syndrome are occasional symptoms
d) Hematuria if develops should treated aggressively

19. A new presented with umbilical stump bleed on evaluation BT. CT and other coagulation tests where normal clot solubility test with urea and trychloro ascetic acid positive. What is the most probable diagnosis.
a) Factor IX deficiency
b) Factor XI deficiency
c) Factor XII deficiency
d) Factor XIII deficiency

20. A child underwent a tonsillectomy at 6 years of age with no complications he underwent a preoperative screening for bleeding at age of 12years before an elective laprotomy and was found to have a prolonged PTT but normal PT. No family history of bleeding. The patient is likely to have.
a) Acquired vitaminK deficiency
b) Acquired liver disease
c) Factor XII deficiency
d) Mild hemophilia

21. Which most likely to be increased in vitamin K deficiency
a) PTT
b) PT
c) Platelet count
d) Fibrinogen time

22. Which of the following is associated with both arterial and venous thrombosis
a) Anti phospho lipid antibody
b) Factor V leiden
c) Antithrombin III deficiency
d) Protein C deficiency

23. Most common coagulation defect in patients with venous thrombosis
a) Factor V leiden
b) Hyper homocystenemia
c) Deficiency of antithrombin III
d) Antiphopholipid antibody syndrome

24. Select incorrect statement about DIC
a) Most frequently associated with obstetric catastrophes, malignancies, Trauma and sepsis
b) Characterized by increased PT, a PTT, TT and FDP
c) Etiology of DIC should be treated first
d) Patients with bleeding treated with FFP and those with thrombosis with heparin
e) None of these
25. Which of the following is not GpIIb/IIIa inhibitor
a) Abciximab
b) Ticlopidine
c) Eptifibatide
d) Tirofiban

26. Select the incorrect statement about unfractionated heparin
a) It is a highly sulfated polysachride obtained form bovine lung or porcine intestinal mucosa

b) Once bound to anti thrombin it pottentiates its anticoagulant effect by inactivation of common pathway coagulation factors, Xa and thrombin
c) Heparin is cleared by RE system, metabolized by liver and products excreted in urine
d) Half life of heparin increase with dose
e) None of these

27. All are true about low molecular weight heparin EXCEPT.
a) Limited antithrombin activity compared to antifactor Xa activity
b) Superior bio availability, limited non specific binding and non dose dependent half life
c) Less incidence of HIT and Osteopenia
d) Neutralized completely by protamine sulfate
e) None of these

28. Select the incorrect statement about HIT
a) Develop in 3% of patients 5 to 10days after onset of treatment
b) Low incidence with LMW heparin
c) Thrombotic complications may precede development of HIT
d) Heparin should be stopped immediately and patient put on warfarin

29. Which of following is not a direct thrombin inhibitor?
a) Fondaparinux
b) Lepirudin
c) Argatroban
d) Ximalagatran

30. Which of following is not a myelo proliferative disorder
a) Polycythemia rubra vera
b) AML
c) CML
d) Essential thrombocytosis

31. Which of the following is not commonly seen in polycythemia vera
a) Thrombosis
b) Hyper urecemia
c) Prone for acute leukemia
d) Spontaneous severe infection

32. All of the following are causes of relative polycythemia EXCEPT.
a) Dehydration
b) Dengue fever
c) Gaisbock syndrome
d) High altitude

33. Which of the following is not used in treatment of polycythemia vera
a) Alkylating agents
b) Iterferon alpha
c) Hydroxurea
d) Anagrelide

34. A patient investigated for anemia has a dry marrow tap peripheral smear reveal tear drops cells likely diagnosis is
a) Leukemia
b) lymphoma
c) Myelofibrosis
d) Polycythemia

35. Which of the following is not a suggested criteria to diagnose essential thrombocytosis
a) Platelet count >5lack
b) Absence of Ph chromosome
c) Absence of marrow iron
d) Normal red cell mass

36. The following statements about maturation of neutrophils are true EXCEPT.
a) Myeloblast is the first recognizable precussor cells and is CD13, CD15 and CD33 positive
b) Primary granules appear in Promyelocyte stage
c) Secondary granules appear in myelocyte stage
d) Secondary granules contain acid hydrolases and is therefore a classic lysosome

37. The following statement about neutrophils are true EXCEPT.
a) Excessive segmentation (>5nuclear lobes) may be a manifestation of folate or vitamin B12 deficiency
b) Band forms have a sausage shaped nucleus
c) Pleger huet anomaly is an infrequent benign inherited trait characterized by neutrophils with bilobed nucleus
d) Dohle bodies and toxic granulations are seen in acute infections
e) None of these

38. All the following causes neutrophilia EXCEPT.
a) Steroids
b) LAD1
c) Wegner's granulomatosis
d) Keto acidosis

39. Select correct statement regarding neutrophil disfunction
a) Most common neutrophil defect is myeloperoxidase deficiency
b) Chidiac higashi syndrome is due to defect in lysosomal transport protein LYST, required for normal packing and dispersement of granules
c) CGD is a an X-linked disease due to lack of 1 of the 4 NADPH oxidase sub unit required for H_2 O_2 production
d) All of these

40. Which of the following is not a TNF alpha inhibitor
a) Bivalizumab
b) Infliximab
c) Etrnacept
d) Adalimumab

41. The following statements about eosinophilia are true EXCEPT.
a) Presence of > 500 eosinophills/micro liter of blood
b) It occurs with stress and after treatment with steroids
c) IL5 is dominant eosinophill growth factor
d) Most severe complication involve heart and CNS

42.Marker of langerhan cell histiocytosis
a) CD1a
b) CD3
c) CD68
d) CD57

43.Drug used in treatment of refractory histiocytosis
a) High dose methotrexate
b) High dose cytarabine
c) Cladrabine
d) Fludrabine

44. all are true about Wiskott Aldrich syndrome except
a) AR
b) Failure of aggregation of platelets in response to agonist
c) Thrombocytopenia
d) Patient presents with eczema

45. NBT test is used for
a) Phagocutosis
b) Compliment
c) T cell
d) B cell

ANEMIAS

1.All the following causes microcytic hypochromic anemias EXCEPT:
a) Lead poisoning
b) Thalassemia
c) Iron deficiency anemia
d) Fanconi's anemia

2.29 old woman was found to have a Hb value of 7.8gm /dl with a reticulocyte count of 0.8% peripheral smear showed microcytic hypochrimic anemia. Hb A_2 and HbF levels were 2.4% and 1.3% respectively. Serum iron 15 micro gm /dl and TIBC 420 micro gm /dl. The most likely cause of anemia is.
a) Iron deficiency
b) anemia of chromic disease
c) β thalassemia
d) Sideroblastic anemia

3.Most sensitive and specific test for diagnosis of iron deficiency anemia
a) Serum iron levels
b) Ferritin level
c) Serum transferrin receptor population
d) Transferrin saturation

4.Iron overload occurs in all EXCEPT:
a) Thalassemia
(b) Myelodisplastic syndrome
c) Polycythemia vera
d) Sideroblastic anemia

5. In anemias caused by renal failure due to the following conditions which has maximum erythropoietin deficiency.
a) Diabetic nephropathy
(b) PCOD
c) HUS
d) Snake Bite

6. True regarding anemia of chronic disease are all EXCEPT:
a) ↓ TIBC
b) ↑ Macrophage iron in marrow
c) ↓ Serum ferritin levels
d) ↓ serum iron level

7. Hb predominantly seen at about 6 weeks of conception are all EXCEPT:
a) Hb portland
b) Hb gower I
c) Hb gower II
d) HbF

8. Mother has sickle cell disease; Father normal chances of children having sickle cell disease and trait respectively.
a) 0 and 100%
b) 25 and 25%
c) 50 and 50%
d) 10 and 50%

9. An 18yr old male undergoing a physical examinations before playing college sports is found to have normal CBC except that MCV is 72fl subsequent testing reveals normal metabisulphate test and normal Hb electrophoresis. Which of following conditions most probably accounts for this condition.

a) HbE trait
b) Sickle cell disease
c) Beta thalassemia trait
d) Alpha thalassemia trait

10. Commonest acute presentation of sickle cell anemia.
a) Painful crises
b) PRIAPISM
c) Isosthenuria
d) Painless hematuria

11.Hydroxurea is used in the treatment of sickle cell anemia because.
a) ↑ HbF levels
b) Suppression of recticulocyte and granulocyte count
d) ↑ NO production
e) All of these

12.Which of the following is not seen in Hb electrophoresis sickle cell anemia
a) HbA
b) HbA_2
c) HbF
d) HbS

13.MC cause of β thalassemia is
a) Mutation causing abberent splicing of mRNA precussor
b) Premature termination of translation of mRNA
c) Deletion of β globulin gene
d) Promoter region mutation

14.A 25 yr old presenting with mild pallor of moderate HSM. Her Hb is 92 dl/l and fetal Hb level is 65%. She has not received any blood transfusion till date.She is most likely suffering from.
a) Thalassemic major
b) Thalassemic intermedia
c) Hereditary persistent fetal Hb
d) Hb D, homozygous state.

15. All are true about β thalassemia minor EXCEPT.
a) Offers resistance against falciparum malaria
b) HbA_2 4-8% is characteristic
c) Screening by NESTROFT and confirmation by S. electrophoresis
d) Manifest 3-9 months after birth when HbF disappears

16.Select the incorrect statement
a) Patients receiving >100 units developed hemosideros usually
b) Vitamin C supplementation helps to decrease iron toxicity
c) SQUID is accurate in measuring hepatic iron
d) Deferiprone is oral iron chelator

17. Diagnosis of β thalassemia is established by
a) NESTROFT test

b) HbA_1 estimation
c) Bone marrow aspiration
d) Hb electrophoreses

18.Macrocytic anemia is seen all following conditions EXCEPT:
a) Liver disease
b) Copper deficiency
c) Orotic aciduria
d) Thiamine deficiency

19. All following statements regarding absorption Vitamin B12 are correct EXCEPT:
a) Intrinsic factor is produced by parital cells of stomach
b) The binding of cobalamine to intrinsic factor after digestion of R binder complex occurs in the stomach
c) Most of vitamin B 12 is absorbed from distal ileum
d) Most circulating cobalamine is bound to a glycoprotein

20.Al following statements about pernicious anemia are true EXCEPT:
a) Most common cause of cobalamine deficiency
b) Association with blood group A
c) H pylori play a key role in parital cell destruction in pernicious anemia
d) Antral sparing is characteristically seen

21.Parasite associated with cobalamine deficiency
a) D latum
b) H.nana
c) P.Westermanni
d) C.Sinnensis

22.Thiamine deficiency is known to occur in all EXCEPT:
a) Food faddist
b) Homocystinemia
c) Chronic alcoholic
d) Chronic heart failure patients on diuretic

23.All are features of megaloblastic anemia EXCEPT:
a) High reticulocyte index
b) Hyper segmented neutrophils
c) Macro ovalocytes
d) Nuclear cytoplasmic asynchrony

24.Hemoglobinuria doesn't occur in
a) Cu SO_4 Poisoning
b) Snake Bite
c) Mismatched Blood transfusion
d) Thalassemia

25.Reticulocytosis is not a feature of
a) PNH
b) Following acute bleeding
c) Hereditary spherocytosis
d) Anemia in CRF

26. Most common cause of AD hereditary spherocytosis is mutation in

a) Spectrin
b) Ankyrin
c) Protein3
d) Protein4.1

27. Features of HS include all the following EXCEPT:
a) Increase osmotic fragility
b) Increase MCHC
c) Increase MCV
d) Decreased surface area/unit volume

28. Splenectomy is most useful in
a) Thrombocytopenia
b) HS
c) HSP
d) Sickle cell anemia

29. Other than HS spherocytes are seen in
a) Autoimmune hemolytic anemia
b) Clostridial infection
c) Snake bite
d) All of these

30. Hemolysis in G6PD deficiency is most often trigged by
a) Infection
b) Drugs
c) Metabolic acidosis
d) Napthelene balls

31. Heinz bodies and bite cells are seen in
a) HS
b) G6PD deficiency
c) Autoimmune hemolytic anemia
d) Thalassemia

32.Which of the following is not an acquired hemolytic anemia
a) Paroxysmal cold hemoglobinuria
b) PNH
c) HUS
d) None of these

33. Warm autoimmune hemolytic anemia may be seen in the following conditions EXCEPT:
(a) SLE
b) Alpha methyl dopa
c) Non hodgkins lymphoma
d) Mycoplasma Pneumonia

34.Auto immune hemolytic anemia is seen in
a) ALL
b) AML
c) CLL
d) CML

35.Coombs positive hemolytic anemia is seen in all EXCEPT.
a) Alcoholic cirrhosis

b) Chronic active hepatitis
c) Primary billiary cirrhosis
d) Primary sclerosing collangits

36.PNH is associated with all following conditions EXCEPT:
a) Aplastic anemia
b) Increased LAP score
c) Venus thrombosis
d) Increasing LDH levels

37.Best investigation for PNH is
a) HAM test
b) Sucrose lysis test
c) Flow cytometry
d) None of these

38. All following statements regarding PNH are true EXCEPT:
a) It is an acquired intrinsic defect in cell membrane
b) Defect is due to mutation in PIGA gene on X-chromosome which is necessary for biosynthesis of GPI anchor
c) There is increased risk of thrombosis
d) Lysis is limited to RBC while platelets and granulocytes are spared

39.All are true about paroxysmal cold hemoglobinuria EXCEPT:
a) Donath landsteiner antibody, an IgG antibody directed against P antigen is responsible
b) Viral infections and auto immune diseases are the most common etiology
c) When secondary to syphilis it responds to therapy for syphilis
d) Respond well to splenectomy

40.Spur cell anemia is seen
a) Linnec cirrhosis
b) Renal failure
c) HUS
d) G6PD deficiency

41.All following causes aplastic anemia EXCEPT:
a) PNH
b) Hepatitis
c) Pregnancy
d) Cold hemoglobinuria

42. Hypocellular bone marrow can be seen in all conditions EXCPET.
a) Q fever
b) Legionnaires disease
c) Leishmaniasis
d) Mycobacterium

43. Vasanthi 25 yr old girl presents with complains of fever and weakness on examination there is splenomegaly of 3.cm below the costal margin.Hb is 8.gm/dl, TLC is 3000, platelet count is 80000, which of the following is least likely diagnosis
a) ALL

b) Anemia of chronic disease
c) Aplastic anemia
d) Megaloblastic anemia

44. A 20 yr old presents with severe hypoplastic anemia what is most effective treatment
a) Alpha interferon
(b) IL2
c) ATG therapy
d) Bone marrow transplantation

45. Most common infection causing aplastic anemia
a) EBV
(b) Hepatitis
c) Parvo virus B19
d) HIV

46.Most early symptom of aplastic anemia
a) Bleeding
b) Infection
c) Symptoms of anemia
d) Weight loss

47. True about MDS is all except
a)Macrocytosis is common, and the smear may be dimorphic with a distinctive population of large red blood cells
b)Ringed sideroblasts seen
c) Sweet's syndrome (febrile neutrophilic dermatosis), occur with MDS
d)None of these

48. Hb X 10 X 10^6 refers to
Red cell count
a) MCV
b) MCH
c) MCHC
d) Hematocrit

49. In a person whose Reticulocyte count is 9%, Hb 7.5gm/dl and hematocrit 23%. What is the absolute Reticulocyte count and Reticulocyte production index
a) 9 & 4.5%
b) 4.5% & 2.25%
c) Both 2.25%
d) 2.25 & 1.125%

50. A patient on evaluation of anemia had a Reticulocyte index <2 and myeloid to erythroid ratio of 1:1. Is most probably having.
a) Hypo proliferative anemia
b) Maturation disorder
c) Hemolytic anemia
d) None these

NEUROLOGY SET - 1

1.Ans C

Table 360-1 Examples of Neurologic Channelopathies	

Category	Disorder	Channel Type
Genetic		
Ataxias	Episodic ataxia-1	K
	Episodic ataxia-2	
	Spinocerebellar ataxia-6	Ca
Migraine	Familial hemiplegic migraine 1	Ca
	Familial hemiplegic migraine 2	Na
Epilepsy	Benign neonatal familial convulsions	K
	Generalized epilepsy with febrile convulsions plus	Na
Periodic paralysis	Hyperkalemic periodic paralysis	Na
	Hypokalemic periodic paralysis	Ca
Myotonia	Myotonia congenita	Cl
	Paramyotonia congenita	Na
Deafness	Jorvell and Lange-Nielsen syndrome (deafness, prolonged QT interval, and arrythmia)	K
	Autosomal dominant progressive deafness	K
Autoimmune		
Paraneoplastic	Limbic encephalitis	Kv1
	Acquired neuromyotonia	Kv1
	Cerebellar ataxia	Ca (P/Q type)
	Lambert-Eaton syndrome	Ca (P/Q type)

2. ANS E

Table 362-6 Common Contraindications to MR Imaging

Cardiac pacemaker or permanent pacemaker leads	McGee stapedectomy piston prosthesis
Internal defibrillatory device	Omniphase penile implant
Cochlear prostheses	Swan-Ganz catheter
Bone growth stimulators	Magnetic stoma plugs
Spinal cord stimulators	Magnetic dental implants
Electronic infusion devices	Magnetic sphincters
Intracranial aneurysm clips (some but not all)	Ferromagnetic IVC filters, coils, stents—safe 6 weeks after implantation
Ocular implants (some) or ocular metallic foreign body	Tattooed eyeliner (contains ferromagnetic material and may irritate eyes)

3. Ans A

- Global symptoms of elevated ICP include headache, which is probably mediated via the pain fibers of cranial nerve (CN) V in the dura and blood vessels,
- Depressed global consciousness due to either the local effect of mass lesions or pressure on the midbrain reticular formation, and vomiting.
- Signs include CN VI palsies, papilledema secondary to impaired axonal transport and congestion, spontaneous periorbital bruising and a triad of bradycardia, respiratory depression, and hypertension (Cushing's triad) .
- Focal symptoms of elevated ICP may be caused by local effects in patients with mass lesions or by herniation syndromes

4 ANS C

- Intraparenchymal hemorrhage is the **most common** type of intracranial hemorrhage.

- **Hypertension**, trauma, and cerebral amyloid angiopathy cause the majority of these hemorrhages
- The most common sites are the basal ganglia (especially the **putamen**), thalamus, cerebellum, and pons.
- When hemorrhages occur in other brain areas or in nonhypertensive patients, greater consideration should be given to hemorrhagic disorders, neoplasms, vascular malformations, and other causes.
- There is growing evidence that intraparenchymal hemorrhage may be exacerbated by acutely elevated blood pressure, and current recommendations are to lower mean arterial blood pressure to <**130 mmHg**
- Embolism is the most common cause for CVA

5 ANS B
SAH

- Excluding head trauma, the most common cause of SAH is rupture of a saccular aneurysm.
- The three most common locations are the terminal internal carotid artery, middle cerebral artery (MCA) bifurcation, and top of the basilar artery.
- Although sudden headachewith neck stiffness in the absence of focal neurologic symptoms is the hallmark of aneurysmal rupture, focal neurologic deficits may occur.
- Thunderclap headache is a variant of migraine that simulates a SAH.
- Mycotic aneurysms are usually located distal to the first bifurcation of major arteries of the circle of Willis. Most result from infected emboli due to bacterial endocarditis causing septic degeneration of arteries and subsequent dilatation and rupture
- The hallmark of aneurysmal rupture is blood in the CSF.
- More than 95% of cases have enough blood to be visualized on a high-quality noncontrast CT scan obtained within 72 h.
- Lysis of the red blood cells and subsequent conversion of hemoglobin to bilirubin stains the spinal fluid yellow within 6–12 h. This xanthochromic spinal fluid peaks in intensity at 48 h.
- Prolonged QRS complex, increased QT interval, and prominent "peaked" or deeply inverted symmetric T waves are usually secondary to the intracranial hemorrhage.
- "Triple-H" (hypertension, hemodilution, and hypervolemic) therapy used in treatment to prevent vasospasm

6 ANS C
Subdural hematoma

- Up to one-third of patients have a lucid interval lasting minutes to hours before coma supervenes.
- Acceleration forces alone, as from whiplash, are sometimes sufficient to produce subdural hemorrhage.
- A subacutely evolving syndrome due to subdural hematoma occurs days or weeks after injury with drowsiness, headache, confusion, or mild hemiparesis.
- On imaging studies subdural hematomas appear as crescentic collections over the convexity of one or both hemispheres, most commonly in the frontotemporal region

7 ANS D

8 ANS B

- Narrowing of the arteries at the base of the brain following SAH causes symptomatic ischemia and infarction in ~30% of patients and is the major cause of delayed morbidity and death.
- Signs of ischemia appear 4–14 days after the hemorrhage, most often at 7 days.
- There are four major causes of delayed neurologic deficits: rerupture, hydrocephalus, vasospasm, and hyponatremia.
- The incidence of rerupture of an untreated aneurysm in the first month following SAH is ~30%, with the peak in the first 7 days.
- Hyponatremia may be profound and can develop quickly in the first 2 weeks following SAH. Both atrial natriuretic peptide and brain natriuretic peptide have a role in producing this "cerebral salt-wasting syndrome."

9 ANS D
The most common *lacunar syndromes* are the following:

(1) *Pure motor hemiparesis* from an infarct in the posterior limb of the internal capsule or basis pontis; the face, arm, and leg are almost always involved;
(2) *Pure sensory stroke* from an infarct in the ventral thalamus;
(3) *Ataxic hemiparesis* from an infarct in the ventral pons or internal capsule;
(4) *Dysarthria and a clumsy hand* or arm due to infarction in the ventral pons or in the genu of the internal capsule
CAUSED BY LIPOHYALINOSIS OF PENETRATING ARTERIES (30- 300 μm)

10 ANS D

- *Anterograde amnesia* which indicates an inability to store, retains, and recalls new knowledge.
- Patients with amnestic states cannot remember what they ate a few minutes ago or the details of an important event they may have experienced a few hours ago.
- In the acute stages, there may also be a tendency to fill in memory gaps with inaccurate, fabricated, and often implausible information. This is known as *confabulation*.
- Medial temporal lobe and hippocampal involvement responsible for acute disturbance of memory

11 ANS D

- The posterior pole of language function is located at the temporoparietal junction and includes a region known as *Wernicke's area*.
- An essential function of Wernicke's area is to transform sensory inputs into their lexical representations so that these can establish the distributed associations that give the word its meaning.
- The anterior pole of the language network is located in the inferior frontal gyrus and includes a region known as *Broca's area*.
- An essential function of this area is to transform lexical representations into their articulatory sequences so that the words can be uttered in the form of spoken language.

12 ANS C

- In pontine hemorrhages, deep coma with quadriplegia usually occurs over a few minutes.
- There is often prominent decerebrate rigidity and "pin-point" (1 mm) pupils that react to light.
- There is impairment of reflex horizontal eye movements evoked by head turning (doll's-head or oculocephalic maneuver) or by irrigation of the ears with ice water.
- Hyperpnea, hyperpyrexia, severe hypertension, and hyperhidrosis are common.
- Death often occurs within a few hours, but small hemorrhages are compatible with survival

13 ANS A

- A deficit of naming (*anomia*) is the single most common finding in aphasic patients
- The lesion sites can be anywhere within the left hemisphere language network, including the middle and inferior temporal gyri.
- *Anomic aphasia is the single most common language disturbance seen in head trauma, metabolic encephalopathy, and Alzheimer's disease*.

14 ANS A

Table 27-1 Clinical Features of Aphasias and Related Conditions

	Comprehension	**Repetition of Spoken Language**	**Naming**	**Fluency**
Wernicke's	Impaired	Impaired	Impaired	Preserved or increased
Broca's	Preserved (except grammar)	Impaired	Impaired	Decreased
Global	Impaired	Impaired	Impaired	Decreased

Conduction	Preserved	Impaired	Impaired	Preserved
Nonfluent (motor) transcortical	Preserved	Preserved	Impaired	Impaired
Fluent (sensory) transcortical	Impaired	Preserved	Impaired	Preserved
Isolation	Impaired	Echolalia	Impaired	No purposeful speech
Anomic	Preserved	Preserved	Impaired	Preserved except for word-finding pauses
Pure word deafness	Impaired only for spoken language	Impaired	Preserved	Preserved
Pure alexia	Impaired only for reading	Preserved	Preserved	Preserved

- Global aphasia –Lt MCA main trunk
- Conduction aphasia – arcuate fasciculus
- Transcortical motor – ant watershed zone
- Transcortical sensory – post watershed zone
- Pure word deafness – sup temporal gyrus
- Alexia without agraphia – splenium of corpus callosum

Gerstmann's syndrome.

- The combination of *acalculia* (impairment of simple arithmetic), *dysgraphia* (impaired writing), *finger anomia* (an inability to name individual fingers such as the index or thumb), and *right-left confusion* (an inability to tell whether a hand, foot, or arm of the patient or examiner is on the right or left side of the body) is known as Gerstmann's syndrome.
- Commonly associated with damage to the inferior parietal lobule (especially the angular gyrus) in the left hemisphere

15 ANS B

- Weber's Syndrome - ipsilateral 3rd nerve paresis and contralateral hemiparesis due to involvement of the pyramidal tract
- Benedikt's/claude Syndrome - ipsilateral 3rd nerve paresis and contralateral hemitremor, due to involvement of the red nucleus or dentate rubro thalamic tract
- Nothnagel's Syndrome - ipsilateral 3rd nerve paresis and cerebellar ataxia, due to involvement of the superior cerebellar peduncle.

16 ANS A

Millard-Gubler Syndrome

A unilateral lesion of the ventrocaudal pons may invovle the basis pontis and the fascicles of cranial nerves VI and VII. Symptoms include:

1. Contralateral hemiplegia (sparing the face) due to pyramidal tract involvement
2. Ipsilateral lateral rectus palsy with diplopia that is accentuated when the patient looks toward the lesion, due to cranial nerve VI involvement.
3. Ipsilateral peripheral facial paresis, due to cranial nerve VII involvement.

Raymonds syndrome

6th CN with contralateral hemiplegia

17 ANS C

18 ANS D

- Lateral medullary syndrome (occlusion of any of five vessels may be responsible—vertebral, posterior inferior cerebellar, superior, middle, or inferior lateral medullary arteries)
- Most cases result from ipsilateral vertebral artery occlusion; in the remainder, PICA occlusion is responsible.

On side of lesion

- Pain, numbness, impaired sensation over half the face: Descending tract and nucleus fifth nerve
- Ataxia of limbs, falling to side of lesion: Uncertain—restiform body, cerebellar hemisphere, cerebellar fibers, spinocerebellar tract (?)
- Nystagmus, diplopia, oscillopsia, vertigo, nausea, vomiting: Vestibular nucleus
- Horner's syndrome (miosis, ptosis, decreased sweating): Descending sympathetic tract
- Dysphagia, hoarseness, paralysis of palate, paralysis of vocal cord, diminished gag reflex: Issuing fibers ninth and tenth nerves
- Loss of taste: Nucleus and tractus solitarius
- Numbness of ipsilateral arm, trunk, or leg: Cuneate and gracile nuclei
- Weakness of lower face: Genuflected upper motor neuron fibers to ipsilateral facial nucleus

On side opposite lesion

- Impaired pain and thermal sense over half the body, sometimes face: Spinothalamic tract

19 ANS A

- *Venous sinus thrombosis* of the lateral or sagittal sinus or of small cortical veins (cortical vein thrombosis) occurs as a complication of oral contraceptive use, pregnancy and the postpartum period, inflammatory bowel disease, intracranial infections (meningitis), and dehydration.
- It is also seen with increased incidence in patients with laboratory-confirmed thrombophilia.
- The venous sinus occlusion is readily visualized using magnetic resonance (MR) venography or conventional x-ray angiography.
- Intravenous heparin, regardless of the presence of intracranial hemorrhage, has been shown to reduce morbidity and mortality, and the long-term outcome is generally good.
- *Moyamoya disease* is a poorly understood occlusive disease involving large intracranial arteries, especially the distal internal carotid artery and the stem of the MCA and ACA.
- Vascular inflammation is absent.
- The lenticulostriate arteries develop a rich collateral circulation around the occlusive lesion, which gives the impression of a "puff of smoke" (*moyamoya* in Japanese) on conventional x-ray angiography.

20 ANS A

Table 364-1 Administration of Intravenous Recombinant Tissue Plasminogen Activator (rtPA) for Acute Ischemic Stroke[a]

Indication	**Contraindication**
Clinical diagnosis of stroke Onset of symptoms to time of drug administration <3 h CT scan showing no hemorrhage or edema of >⅓ of the MCA territory Age >18 years Consent by patient or surrogate	Sustained BP >185/110 despite treatment Platelets <100,000; HCT <25%; glucose <50 or >400 mg/dL Use of heparin within 48 h and prolonged PTT, or elevated INR Rapidly improving symptoms Prior stroke or head injury within 3 months; prior intracranial hemorrhage Major surgery in preceding 14 days Minor stroke symptoms Gastrointestinal bleeding in preceding 21 days Recent myocardial infarction Coma or stupor
Administration of rtPA Intravenous access with two peripheral IV lines (avoid arterial or central line placement) Review eligibility for rtPA Administer 0.9 mg/kg intravenously (maximum 90 mg) IV as 10% of total dose by bolus, followed by remainder of total dose over 1 h Frequent cuff blood pressure monitoring No other antithrombotic treatment for 24 h For decline in neurologic status or uncontrolled blood pressure, stop infusion, give cryoprecipitate, and reimage brain emergently	

Avoid urethral catheterization for 2 h

21 ANS B
Relatively few cranial structures are pain-producing; these include the scalp, middle meningeal artery, dural sinuses, falx cerebri, and proximal segments of the large pial arteris
Migraine

- Classical migraine – with aura
- Common migraine – without aura
- All age groups
- More common in females
- Family history may be present
- Decreased by sleep
- Usually lateralized
- Migraine sine migraine – visual disturbances without headache
- Opthalmoplegic migraine-transient 3rd nerve palsy

Prophylaxis

- Beta blockers
- TCA
- Anti convulsants – valproate; topiramate; gabapentin
- Serotenergic – methysergide; flunarezine
- Pizotifen

Cluster Headache	
Gender	M>F
Pain	
Type	Stabbing, boring
Severity	Excruciating
Site	Orbit, temple
Attack frequency	1/alternate day– 8/d
Duration of attack	15–180 min
Autonomic features	Yes
Migrainous features[b]	Yes
Alcohol trigger	Yes
Cutaneous triggers	No
Indomethacin effect	—
Abortive treatment	Sumatriptan injection or nasal spray Oxygen
Prophylactic treatment	Verapamil Methysergide Lithium

Temporal arteritis

- Elderly
- Elavated ESR
- More common in females
- Symptoms include headache, polymyalgia rheumatica , jaw claudication, fever, and weight loss
- Untreated patients develop vision loss due to opthalmic artery involvement
- Temporal artery biopsy
- Prednisolone prevents ischemic optic neuropathy

Tension headache

- Chronic head pain syndrome
- Generalized headache
- Exacerbated by emotions
- A useful clinical approach is to diagnose TTH in patients whose headaches are completely without accompanying features such as nausea, vomiting, photophobia, phonophobia, osmophobia, throbbing, and aggravation with movement

22 ANS A

- Absence seizures are characterized by sudden, brief lapses of consciousness without loss of postural control.
- The seizure typically lasts for only seconds, consciousness returns as suddenly as it was lost, and there is no postictal confusion.
- Absence seizures usually begin in childhood (ages 4–8) or early adolescence.
- The electrophysiologic hallmark of typical absence seizures is a generalized, symmetric, 3-Hz spike-and-wave discharge that begins and ends suddenly, superimposed on a normal EEG background.. respond well to treatment with specific anticonvulsants.
- 60–70% of such patients will have a spontaneous remission during adolescence.

23 ANS A

- Juvenile myoclonic epilepsy (JME) is a generalized seizure disorder of unknown cause that appears in early adolescence and is usually characterized by bilateral myoclonic jerks that may be single or repetitive.
- The condition is otherwise benign, and although complete remission is uncommon, the seizures respond well to appropriate anticonvulsant medication

24 ANS A

25 ANS D

- Neurological – Dizziness,Diplopia,Ataxia,Incoordination,Confusion
- Systemic - Gum hyperplasia,Lymphadenopathy,Hirsutism,Osteomalacia,Facial coarsening,Skin rash

26 ANS D

27 ANS B

Table 363-3 Characteristics of the Mesial Temporal Lobe Epilepsy Syndrome	
History	
History of febrile seizures	Rare secondarily generalized seizures
Family history of epilepsy	Seizures may remit and reappear
Early onset	Seizures often intractable
Clinical observations	
Aura common	Postictal disorientation, memory loss, dysphasia (with focus in dominant hemisphere)
Behavioral arrest/stare	
Complex automatisms	
Unilateral posturing	
Laboratory studies	
Unilateral or bilateral anterior temporal spikes on EEG	

Hypometabolism on interictal PET
Hypoperfusion on interictal SPECT
Material-specific memory deficits on intracranial amobarbital (Wada) test
MRI findings
Small hippocampus with increased signal on T2-weighted sequences
Small temporal lobe
Enlarged temporal horn
Pathologic findings
Highly selective loss of specific cell populations within hippocampus in most cases

28 ANS A

Table 363-8 Selection of Antiepileptic Drugs

Primary Generalized Tonic-Clonic	**Partial[a]**	**Absence**	**Atypical Absence, Myoclonic, Atonic**
First-Line			
Valproic acid Lamotrigine Topiramate	Carbamazepine Phenytoin Lamotrigine Oxcarbazepine Valproic acid	Valproic acid Ethosuximide	Valproic acid Lamotrigine Topiramate

29 ANS C

30 ANS E

31 ANS C

- AD can occur in any decade of adulthood, but it is the most common cause of dementia in the elderly.
- Pathologically, there is diffuse atrophy of the cerebral cortex with secondary enlargement of the ventricular system.
- Microscopically, there are neuritic plaques containing Aβ amyloid, silver-staining neurofibrillary tangles (NFTs) in neuronal cytoplasm, and accumulation of A_β amyloid in arterial walls of cerebral blood vessels
- The most important risk factors for AD are old age and a positive family history.
- Female gender, low educational attainment, Numerous environmental factors, including aluminum, mercury, and viruses, Elevated homocysteine and cholesterol levels; hypertension; diminished serum levels of folic acid; low dietary intake of fruits, vegetables, and red wine; and low levels of exercise are all being explored as potential risk factors for AD.
- Diabetes increases the risk of AD threefold.
- Several genetic factors play important roles in the pathogenesis of at least some cases of AD. One is the *APP* gene on chromosome 21.
- Adults with trisomy 21 (Down's syndrome) consistently develop the typical neuropathologic hallmarks of AD if they survive beyond age 40.
- Several studies suggest that the use of nonsteroidal anti-inflammatory agents is associated with a decreased risk of AD

32 ANS C

- The most severe pathology is usually found in the hippocampus, temporal cortex, and nucleus basalis of Meynert (lateral septum).
- The most important microscopic findings are neuritic "senile" plaques and NFTs.
- These lesions accumulate in small numbers during normal aging of the brain but occur in excess in AD.

- There is increasing evidence to suggest that soluble amyloid fibrils called *oligomers* lead to the dysfunction of the cell and may be the first biochemical injury in AD.
- Misfolded $A\beta_{42}$ molecules may be the most toxic form of this protein.
- Accumulation of oligomers eventually leads to formation of neuritic plaques.
- The neuritic plaques contain a central core that includes Aβ amyloid, proteoglycans.
- Aβamyloid is a protein of 39–42 amino acids that is derived proteolytically from a larger transmembrane protein named *amyloid precursor protein* (APP) which has neurotrophic and neuroprotective activities.
- The accumulation of Aβamyloid in cerebral arterioles is termed *amyloid angiopathy*.
- NFTs are silver staining, twisted neurofilaments in neuronal cytoplasm that represent abnormally phosphorylated tau protein and appear as paired helical filaments by electron microscopy.
- Tau is a microtubule associated protein that may function to assemble and stabilize the microtubules that convey cell organelles, glycoproteins, and other important materials throughout the neuron. Increased phosphorylation of tau protein disturbs this normal process
- Biochemically, AD is associated with a decrease in the cerebral cortical levels of several proteins and neurotransmitters, especially acetylcholine, its synthetic enzyme choline acetyltransferase, and nicotinic cholinergic receptors.

33 ANS B

- Reduction of acetylcholine may be related in part to degeneration of cholinergic neurons in the nucleus basalis of Meynert that project to many areas of cortex

34 ANS C

- Donepezil, rivastigmine, galantamine, memantine, and tacrine are the drugs presently approved by the Food and Drug Administration (FDA) for treatment of AD.
- Due to hepatotoxicity, tacrine is no longer used.
- The pharmacologic action of donepezil, rivastigmine, and galantamine is inhibition of cholinesterase, with a resulting increase in cerebral levels of acetylcholine.
- Memantine appears to act by blocking overexcited N-methyl-D-aspartate (NMDA) channels.
- A randomized, double-blind, placebo-controlled trial of an extract of *Ginkgo biloba* found modest improvement in cognitive function in subjects with AD and vascular dementia
- Several retrospective studies suggest that nonsteroidal anti-inflammatory agents and statins (HMG-CoA reductase inhibitors) may have a protective effect on dementia, and controlled prospective studies are being conducted.
- Vaccination against $A\beta_{42}$ has proved highly efficacious in mouse models of AD; it helped to clear amyloid from the brain and prevent further accumulation of amyloid. However, in human trials this approach led to life-threatening complications, including meningoencephalitis
- Antioxidants selegiline ,alpha tocopherol (vitamin E), estrogen replacement therapy-doubtful role

35 ANS C

Table 365-2 The Molecular Basis for Degenerative Dementia

Dementia	**Molecular Basis**	**Causal Genes and (Chromosome)**	**Susceptibility Genes**	**Pathology**
AD	Aβ	<2% carry these mutations.	*Apo ε4* (19)	Amyloid plaques, neurofibrillary tangles
		APP (21), *PS-1* (14), *PS-2* (1) (most mutations are in *PS-1*)		
FTD	Tau	Tau exon and intron mutations (17) (about 10% of familial cases)	H1 tau haplotypes	Tau inclusions, Pick bodies, neurofibrillary tangles

		Progranulin (17) (10% of familial cases)		
DLB	α-synuclein	Very rare α-synuclein (4) (dominant)	Unknown	α-synuclein inclusions (Lewy bodies)
CJD	PrP^{SC} proteins	Prion (20) (up to 15% of cases carry these dominant mutations)	Codon 129 homozygosity for methionine or valine	Tau inclusions, spongiform changes, gliosis

36 ANS C

- Approximately 10% of AD patients develop *Capgras' syndrome*, believing that a caregiver has been replaced by an impostor.
- In contrast to DLB, where Capgras' syndrome is an early feature, in AD this syndrome emerges later in the course of the illness.

Dementia with Lewy Bodies

- The parkinsonian dementia syndromes are under increasing study, with many cases unified by the presence of Lewy bodies in both the substantia nigra and the cortex at pathology.
- The clinical syndrome is characterized by visual hallucinations, parkinsonism, fluctuating alertness, falls, and often REM sleep behavior disorder.
- Dementia can precede or follow the appearance of parkinsonism
- Cognitively, DLB patients tend to have relatively better memory but more severe visuospatial deficits than individuals with AD.
- The key neuropathologic feature is the presence of Lewy bodies throughout the cortex, amygdala, cingulate cortex, and substantia nigra.
- Lewy bodies are intraneuronal cytoplasmic inclusions that stain with periodic acid–Schiff (PAS) and ubiquitin.
- They are composed of straight neurofilaments 7–20 nm long with surrounding amorphous material.
- They contain epitopes recognized by antibodies against phosphorylated and nonphosphorylated neurofilament proteins, ubiquitin, and a presynaptic protein called α-synuclein.
- In patients whose brains also contain excessive amounts of amyloid plaques and NFTs, the condition is called the *Lewy body variant of Alzheimer's disease*

Table 365-4 Clinical Differentiation of the Major Dementias

Disease	**First Symptom**	**Mental Status**	**Neuropsychiatry**	**Neurology**	**Imaging**
AD	Memory loss	Episodic memory loss	Initially normal	Initially normal	Entorhinal cortex and hippocampal atrophy
FTD	Apathy; poor judgment/insight, speech/language; hyperorality	Frontal/executive, language; spares drawing	Apathy, disinhibition, hyperorality, euphoria, depression	Due to PSP/CBD overlap; vertical gaze palsy, axial rigidity, dystonia, alien hand	Frontal and/or temporal atrophy; spares posterior parietal lobe

DLB	Visual hallucinations, REM sleep disorder, delirium, Capgras' syndrome, parkinsonism	Drawing and frontal/executive; spares memory; delirium prone	Visual hallucinations, depression, sleep disorder, delusions	Parkinsonism	Posterior parietal atrophy; hippocampi larger than in AD
CJD	Dementia, mood, anxiety, movement disorders	Variable, frontal/executive, focal cortical, memory	Depression, anxiety	Myoclonus, rigidity, parkinsonism	Cortical ribboning and basal ganglia or thalamus hyperintensity on diffusion/flare MRI
Vascular	Often but not always sudden; variable; apathy, falls, focal weakness	Frontal/executive, cognitive slowing; can spare memory	Apathy, delusions, anxiety	Usually motor slowing, spasticity; can be normal	Cortical and/or subcortical infarctions, confluent white matter disease

37 ANS A
Treatable dementias
Hypothyroidism ;Thiamine deficiency ;Vitamin B12 deficiency ; Normal-pressure hydrocephalus ; Subdural hematoma ;Chronic infection ;Brain tumor ;Drug intoxication
38 ANS

- HD is a progressive, fatal, autosomal dominant disorder characterized by motor, behavioral, and cognitive dysfunction.
- Onset is typically between the ages of 25 and 45 years (range 3–70 years).
- Neuropathologically, the disease predominantly strikes the striatum.
- Atrophy of the caudate nuclei, which form the lateral margins of the lateral ventricles, can be visualized on neuroimaging studies.
- Relative under activity of neurons containing GABA and actyl choline.
- HD is caused by an increase in the number of polyglutamine (CAG) repeats (>40) in the coding sequence of the Huntington gene located on the short arm of chromosome 4.
- The larger the number of repeats, the earlier the disease is manifest.
- Anticipation occurs, particularly in males, with subsequent generations having larger numbers of repeats and earlier age of disease onset.
- The gene encodes the highly conserved cytoplasmic protein huntingtin, which is widely distributed in neurons throughout the CNS, but whose function is not known.
- Intraneuronal inclusions containing aggregates of ubiquitin and the mutant protein huntingtin are found in nuclei of neurons in the striatum and cerebral cortex

39 ANS A
(1) Prions are the only known infectious pathogens that are devoid of nucleic acid; all other infectious agents possess genomes composed of either RNA or DNA that direct the synthesis of their progeny.
(2) Prion diseases may be manifest as infectious, genetic, and sporadic disorders; no other group of illnesses with a single etiology presents with such a wide spectrum of clinical manifestations.
(3) Prion diseases result from the accumulation of PrP^{Sc}, the conformation of which differs substantially from that of its precursor, PrP^{C}.
(4) PrP^{Sc} can exist in a variety of different conformations, each of which seems to specify a particular disease phenotype.
CJD

- Most common prion disease
- Visual symptoms early
- Rapidly progressing dementia
- Myoclonus in 90%

- Death in 6-12 months
- EEG shows periodic high amplitude triphasic sharp discharges
- CSF shows elevated stress protien 14-3-3
- FLAIR- cortical ribboning and increased intensity in basal ganglia
- Confirmatory –PrPsc in brain biopsy

40 ANS A

- For NPH the clinical triad includes an abnormal gait (ataxic or apractic), dementia (usually mild to moderate), and urinary incontinence.
- Neuroimaging studies reveal enlarged lateral ventricles (hydrocephalus) with little or no cortical atrophy.
- This syndrome is a communicating hydrocephalus with a patent aqueduct of Sylvius , in contrast to congenital aqueductal stenosis, where the aqueduct is small.
- In many cases, periventricular edema is present.
- Lumbar puncture opening pressure is in the high normal range, and the CSF protein, sugar concentrations, and cell count are normal.
- NPH is presumed to be caused by obstruction to normal flow of CSF over the cerebral convexity and delayed absorption into the venous system.
- The indolent nature of the process results in enlarged lateral ventricles but relatively little increase in CSF pressure.
- There is sometimes a transient improvement in gait or cognition following lumbar puncture (or serial punctures) with removal of 30–50 mL of CSF, but this finding also has not proven to be consistently predictive of post-shunt improvement.
- AD often masquerades as NPH, because the gait may be abnormal in AD and cortical atrophy sometimes is difficult to determine by CT or MRI early in the disease.
- Hippocampal atrophy on MRI is a clue favoring AD.
- Approximately 30–50% of patients identified by careful diagnosis as having NPH will show improvement with a ventricular shunting procedure

41 ANS A

- Wernicke's disease is a common and preventable disorder due to a deficiency of thiamine.
- Alcoholics account for most cases, but patients with malnutrition due to hyperemesis, starvation, renal dialysis, cancer, AIDS, or rarely gastric surgery are also at risk.
- The characteristic clinical triad is that of ophthalmoplegia, ataxia, and global confusion.
- Patients who recover show improvement in ocular palsies within hours after the administration of thiamine, but horizontal nystagmus may persist.
- Ataxia improves more slowly.
- As these symptoms recede, an amnestic state with impairment in recent memory and learning may become more apparent (*Korsakoff's psychosis*).
- Korsakoff's psychosis is frequently persistent.
- Periventricular lesions surround the third ventricle, aqueduct, and fourth ventricle, with petechial hemorrhages in occasional acute cases and atrophy of the mamillary bodies in most chronic cases.
- The amnestic defect is related to lesions in the dorsal medial nuclei of the thalamus.
- Thiamine deficiency produces a diffuse decrease in cerebral glucose utilization and results in mitochondrial damage.
- Glutamate accumulates owing to impairment of α-ketoglutarate dehydrogenase activity and, in combination with the energy deficiency, may result in excitotoxic cell damage.
- Wernicke's disease is a medical emergency and requires immediate administration of thiamine, in a dose of 100 mg either IV or IM

42 ANS B

- Idiopathic intracranial hypertension (IIH) is also commonly called pseudotumor cerebri.
- It is a disorder defined by clinical criteria that include symptoms and signs isolated to those produced by increased intracranial pressure (eg, headache, papilledema, vision loss), elevated intracranial pressure with

normal cerebrospinal fluid composition, and no other cause of intracranial hypertension evident on neuroimaging or other evaluations

- Headache is the most common presenting symptom of IIH.
- The most common signs in IIH are Papilledema ,Visual field loss ,Sixth nerve palsy

43 ANS D

44 ANS A
PARKINSONS DISEASE

- Disturbance in substantia nigra
- 4-6 hz rest tremor
- Normal DTR
- Festinating gait
- Small hand writing
- Normal IQ
- Expression less facies
- Cogwheel rigidity
- Postural reflexes lost

45 ANS C

- DOC for drug induced parkinsonism – central anti cholinergics like trihexiphenidyl

NEUROLOGY SET - 2

1.ANS B
Huntington's Disease

- HD is a progressive, fatal, autosomal dominant disorder characterized by motor, behavioral, and cognitive dysfunction
- A clinical diagnosis of HD can be strongly suspected in cases of chorea with a positive family history.
- HD is caused by an increase in the number of polyglutamine (CAG) repeats (>40) in the coding sequence of the Huntington gene located on the short arm of chromosome 4.
- The gene encodes the highly conserved cytoplasmic protein huntingtin, which is widely distributed in neurons throughout the CNS, but whose function is not known
- Neuropathologically, the disease predominantly strikes the striatum. Atrophy of the caudate nuclei, which form the lateral margins of the lateral ventricles
- Genetic testing can be used to confirm the diagnosis and to detect affected individuals in the family, but this should be performed with caution and in conjunction with trained counselors, as positive results can lead to depressive and suicidal reactions.

2.ANS A

Table 367-1 Hyperkinetic Movement Disorders

Disorders	**Movement Characteristics**
Athetosis	Slow, distal, writhing, involuntary movements with a propensity to affect the arms and hands.
Chorea	Rapid, semipurposeful, graceful, dancelike, nonpatterned involuntary movements involving distal or proximal muscle groups.
Dystonia	Involuntary patterned sustained or repeated muscle contractions, often leading to twisting movements and abnormal posture.
Myoclonus	Sudden, brief (<100 ms), shocklike, arrhythmic muscle twitches.
Tics	Brief, repeated, stereotyped muscle contractions that are often suppressible. Can be simple and involve a single muscle group or complex and affect a range of motor activities.
Tremor	Rhythmic oscillation of a body part due to intermittent muscle contractions.

3.ANS D

- The tremor characteristically improves with alcohol and may worsen with stress
- ET can be differentiated from Parkinson's disease (PD) by the absence of resting tremor, bradykinesia, rigidity, micrographia, and other parkinsonian features.
- Tremor can also be observed with a variety of drugs, multiple sclerosis, degenerative disorders, and metabolic alterations.
- Approximately 50% of cases have a positive family history with an autosomal dominant pattern of inheritance
- Primidone (25–1000 mg/d) and propranolol (20–80 mg/d) are the standard drug therapies

4.ANS D

5.ANS D

- Negative myoclonus consists of a twitch due to a brief loss of muscle activity (e.g., asterixis in hepatic failure)

6.ANS B

Table 368-1 Etiology of Cerebellar Ataxia

Symmetric and Progressive Signs			**Focal and Ipsilateral Cerebellar Signs**		
Acute (Hours to Days)	**Subacute (Days to Weeks)**	**Chronic (Months to Years)**	**Acute (Hours to Days)**	**Subacute (Days to Weeks)**	**Chronic (Months to Years)**
Intoxication: alcohol, lithium, diphenylhydantoin, barbiturates (positive history and toxicology screen)	Intoxication: mercury, solvents, gasoline, glue; cytotoxic chemotherapeutic drugs	Paraneoplastic syndrome Anti-gliadin antibody syndrome Hypothyroidism	Vascular: cerebellar infarction, hemorrhage, or subdural hematoma Infectious: cerebellar abscess (mass lesion on MRI/CT, history in support of lesion)	Neoplastic: cerebellar glioma or metastatic tumor (positive for neoplasm on MRI/CT) Demyelinating: multiple sclerosis (history, CSF, and MRI are consistent)	Stable gliosis secondary to vascular lesion or demyelinating plaque (stable lesion on MRI/CT older than several months)
Acute viral cerebellitis (CSF supportive of acute viral infection) Postinfection syndrome	Alcoholic-nutritional (vitamin B_1 and B_{12} deficiency) Lyme disease	Inherited diseases Tabes dorsalis (tertiary syphilis) Phenytoin toxicity		AIDS-related multifocal leukoencephalopathy (positive HIV test and CD4+ cell count for AIDS)	Congenital lesion: Chiari or Dandy-Walker malformations (malformation noted on MRI/CT

7.ANS A

- The autosomal spinocerebellar ataxias (SCAs) include SCA types 1 through SCA28, dentatorubropallidoluysian atrophy (DRPLA), and episodic ataxia (EA) types 1 and 2 .
- SCA1, SCA2, SCA3 [Machado-Joseph disease (MJD)], SCA6, SCA7, and SCA17 are caused by CAG triplet repeat expansions in different genes.
- SCA8 is due to an untranslated CTG repeat expansion,
- SCA10 is caused by an untranslated pentanucleotide repeat
- CAG encodes glutamine, and these expanded CAG triplet repeat expansions result in expanded polyglutamine proteins, termed *ataxins*, that produce a toxic gain of function with autosomal dominant inheritance

8.ANS D

- Different mutations in the same gene for the α_{1A} voltage-dependent calcium channel subunit (CACNLIA4; also referred to as the *CACNA1A* gene) at 19p13 result in different clinical disorders.
- CAG repeat expansions (21–27 in patients; 4–16 triplets in normal individuals) result in late-onset progressive ataxia with cerebellar degeneration –SCA 6.
- Missense mutations in this gene result in familial hemiplegic migraine.
- Nonsense mutations resulting in termination of protein synthesis of the gene product yield hereditary paroxysmal cerebellar ataxia or EA 2.

9.ANS B

- This is the most common form of inherited ataxia, comprising one-half of all hereditary ataxias.
- It can occur in a classic form or in association with a genetically determined vitamin E deficiency syndrome
- Friedreich's ataxia presents before 25 years of age with progressive staggering gait, frequent falling, and titubation.
- Extensor plantar responses (with normal tone in trunk and extremities), absence of deep tendon reflexes, and weakness (greater distally than proximally) are usually found. Loss of vibratory and proprioceptive sensation occurs.
- The median age of death is 35 years. Women have a significantly better prognosis than men.
- Cardiac involvement occurs in 90% of patients
- A high incidence of diabetes mellitus (20%) is found
- Musculoskeletal deformities are common and include pes cavus, pes equinovarus, and scoliosis.
- MRI of the spinal cord shows atrophy
- The primary sites of pathology are the spinal cord, dorsal root ganglion cells, and the peripheral nerves . Sclerosis and degeneration occur predominantly in the spinocerebellar tracts, lateral corticospinal tracts, and posterior columns
- The mutant gene, *frataxin*, contains expanded GAA triplet repeats

10.ANS D

Table 369-2 Sporadic Motor Neuron Diseases
Chronic
Upper and lower motor neurons Amyotrophic lateral sclerosis Predominantly upper motor neurons Primary lateral sclerosis Predominantly lower motor neurons Multifocal motor neuropathy with conduction block Motor neuropathy with paraproteinemia or cancer Motor-predominant peripheral neuropathies Other Associated with other degenerative disorders Secondary motor neuron disorders
Acute
Poliomyelitis Herpes zoster Coxsackie virus

11.ANS D

- It is characteristic of ALS that, regardless of whether the initial disease involves upper or lower motor neurons, both will eventually be implicated.
- Even in the late stages of the illness, sensory, bowel and bladder, and cognitive functions are preserved.
- Even when there is severe brainstem disease, ocular motility is spared until the very late stages of the illness.
- Dementia is not a component of sporadic ALS. In some families, ALS is co-inherited with frontotemporal dementia

12.ANS E

- No treatment arrests the underlying pathologic process in ALS.
- The drug riluzole (100 mg/d) was approved for ALS because it produces a modest lengthening of survival
- riluzole may reduce excitotoxicity by diminishing glutamate release.
- Interventions such as antisense oligonucleotides (ASO) or inhibitory RNA that diminish expression of mutant SOD1 protein prolong survival in transgenic ALS mice

13.ANS C

- The SMAs are a family of selective lower motor neuron diseases of early onset.
- Neuropathologically these disorders are characterized by extensive loss of large motor neurons; muscle biopsy reveals evidence of denervation atrophy
- Infantile SMA (SMA I, Werdnig-Hoffmann disease) has the earliest onset and most rapidly fatal course. In some instances it is apparent even before birth, as indicated by decreased fetal movements late in the third trimester. Though alert, afflicted infants are weak and floppy (hypotonic) and lack muscle stretch reflexes. Death generally ensues within the first year of life.
- Chronic childhood SMA (SMA II) begins later in childhood and evolves with a more slowly progressive course.
- Juvenile SMA (SMA III, Kugelberg-Welander disease) manifests during late childhood and runs a slow, indolent course. Unlike most denervating diseases, in this chronic disorder weakness is greatest in the **proximal muscles**; indeed, the pattern of clinical weakness can suggest a primary myopathy such as limb-girdle dystrophy. Electrophysiologic and muscle biopsy evidence of denervation distinguish SMA III from the myopathic syndromes.

14.ANS B

Table 370-1 Functional Consequences of Normal ANS Activation

	Sympathetic	**Parasympathetic**
Heart rate	Increased	Decreased
Blood pressure	Increased	Mildly decreased
Bladder	Increased sphincter tone	Voiding (decreased tone)
Bowel motility	Decreased motility	Increased
Lung	Bronchodilation	Bronchoconstriction
Sweat glands	Sweating	—
Pupils	Dilation	Constriction
Adrenal glands	Catecholamine release	—
Sexual function	Ejaculation, orgasm	Erection
Lacrimal glands	—	Tearing
Parotid glands	—	Salivation

15.ANS D

- Acetylcholine (ACh) is the preganglionic neurotransmitter for both divisions of the ANS as well as the postganglionic neurotransmitter of the parasympathetic neurons.

- Norepinephrine (NE) is the neurotransmitter of the postganglionic sympathetic neurons, except for cholinergic neurons innervating the eccrine sweat glands.

16.ANS B

- Trigeminal neuralgia is characterized by excruciating paroxysms of pain in the lips, gums, cheek, or chin and, very rarely, in the distribution of the ophthalmic division of the fifth nerve.
- The pain seldom lasts more than a few seconds or a minute or two but may be so intense that the patient winces, hence the term *tic*.
- Another characteristic feature is the presence of trigger zones, typically on the face, lips, or tongue, that provoke attacks
- An essential feature of trigeminal neuralgia is that objective signs of sensory loss cannot be demonstrated on examination.

17.ANS D

18.ANS A

Table 372-2 Spinal Cord Levels Relative to the Vertebral Bodies	
Spinal Cord Level	**Corresponding Vertebral Body**
Upper cervical	Same as cord level
Lower cervical	1 level higher
Upper thoracic	2 levels higher
Lower thoracic	2 to 3 levels higher
Lumbar	T10-T12
Sacral	T12-L1

19.ANS C

Central Cord Syndrome

- The central cord syndrome results from damage to the gray matter nerve cells and crossing spinothalamic tracts near the central canal.
- In the cervical cord, the central cord syndrome produces arm weakness out of proportion to leg weakness and a "dissociated" sensory loss, signifying a loss of pain and temperature sense in a cape distribution over the shoulders, lower neck, and upper trunk in contrast to preservation of light touch, joint position, and vibration sense in these regions.
- Trauma, syringomyelia, tumors, and anterior spinal artery ischemia (including from aortic dissection) are the main causes.

Brown-Sequard Hemicord Syndrome

- This consists of ipsilateral weakness (corticospinal tract) and loss of joint position and vibratory sense (posterior column), with contralateral loss of pain and temperature sense (spinothalamic tract) one or two levels below the lesion.
- Segmental signs, such as radicular pain, muscle atrophy, or loss of a deep tendon reflex, are unilateral

Anterior Spinal Artery Syndrome

- Infarction of the cord is generally the result of occlusion or diminished flow in this artery.
- The result is extensive bilateral tissue destruction that spares the posterior columns.
- All spinal cord functions—motor, sensory, and autonomic—are lost below the level of the lesion, with the striking exception of retained vibration and position sensation.

20.ANS D

- With extramedullary lesions, radicular pain is often prominent, and there is early sacral sensory loss (lateral spinothalamic tract) and spastic weakness in the legs (corticospinal tract) due to the superficial location of leg fibers in the corticospinal tract.
- Intramedullary lesions tend to produce poorly localized burning pain rather than radicular pain and spare sensation in the perineal and sacral areas ("sacral sparing"), reflecting the laminated configuration of the spinothalamic tract with sacral fibers outermost; corticospinal tract signs appear later

21.ANS D

- Infections of the spinal column (osteomyelitis and related disorders) are distinctive in that, unlike tumor, they may cross the disk space to involve the adjacent vertebral body.

22.ANS A

- The cord is supplied by three arteries that course vertically over its surface: a single anterior spinal artery and paired posterior spinal arteries.
- In addition to the vertebral arteries, the anterior spinal artery is fed by radicular vessels that arise at C6, at an upper thoracic level, and, most consistently, at T11-L2 (artery of Adamkiewicz)

23.ANS E

- Syringomyelia is a developmental cavitary expansion of the cervical cord that is prone to enlarge and produce progressive myelopathy
- More than half of all cases are associated with Chiari type 1 malformations in which the cerebellar tonsils protrude through the foramen magnum and into the cervical spinal canal
- Acquired cavitations of the cord in areas of necrosis are also termed *syrinx cavities*; these follow trauma, myelitis, necrotic spinal cord tumors, and chronic arachnoiditis due to tuberculosis and other etiologies
- The classic presentation is a central cord syndrome consisting of a dissociated sensory loss and areflexic weakness in the upper limbs
- As the cavity enlarges and further compresses the long tracts, spasticity and weakness of the legs, bladder and bowel dysfunction, and a Horner's syndrome appear

24.ANS D

- This treatable myelopathy presents with subacute paresthesias in the hands and feet, loss of vibration and position sensation, and a progressive spastic and ataxic weakness.
- Loss of reflexes due to an associated peripheral neuropathy in a patient who also has Babinski signs, is an important diagnostic clue.
- Optic atrophy and irritability or other mental changes may be prominent in advanced cases.
- The myelopathy of subacute combined degeneration tends to be diffuse rather than focal; signs are generally symmetric and reflect predominant involvement of the posterior and lateral tracts, including Romberg's sign.
- The diagnosis is confirmed by the finding of macrocytic red blood cells, a low serum B_{12} concentration, elevated serum levels of homocysteine and methylmalonic acid, and in uncertain cases a positive Schilling test

25.ANS A

- The characteristic symptoms of tabes are fleeting and repetitive lancinating pains, primarily in the legs or less often in the back, thorax, abdomen, arms, and face.
- Ataxia of the legs and gait due to loss of position sense occurs in half of patients.
- Paresthesias, bladder disturbances, and acute abdominal pain with vomiting (visceral crisis) occur in 15–30% of patients.
- The cardinal signs of tabes are loss of reflexes in the legs; impaired position and vibratory sense; Romberg's sign; and, in almost all cases, bilateral Argyll Robertson pupils, which fail to constrict to light but accommodate

Asymptomatic Neurosyphilis

- The diagnosis of asymptomatic neurosyphilis is made in patients who lack neurologic symptoms and signs but who have CSF abnormalities including mononuclear pleocytosis, increased protein concentrations, or a reactive Venereal Disease Research Laboratory (VDRL) slide test.
- Such abnormalities are found in up to one-quarter of patients with untreated latent syphilis, and these patients are at risk for development of neurologic complications.
- In primary and secondary syphilis, such abnormalities may be found in up to 40% of untreated patients, and *T. pallidum* can be isolated from CSF of 30% of patients even in the absence of other CSF abnormalities

Symptomatic Neurosyphilis

- Although mixed features are common, the major clinical categories of symptomatic neurosyphilis include meningeal, meningovascular, and parenchymatous syphilis.
- The last category includes general paresis and tabes dorsalis.
- The onset of symptoms usually comes <1 year after infection for meningeal syphilis, at 5–10 years for meningovascular syphilis, at 20 years for general paresis, and at 25–30 years for tabes dorsalis.

26.ANS B

- Multiple sclerosis (MS) is characterized by a triad of inflammation, demyelination, and gliosis (scarring)
- MS is approximately threefold more common in women than men.
- The age of onset is typically between 20 and 40 years
- Heat sensitivity refers to neurologic symptoms produced by an elevation of the body's core temperature. For example, unilateral visual blurring may occur during a hot shower or with physical exercise (Uhthoff's symptom)
- Lhermitte's symptom is an electric shocklike sensation (typically induced by flexion or other movements of the neck) that radiates down the back into the legs.
- 4 CLINICAL TYPES
  - Relapsing/remitting MS (RRMS)
  - Secondary progressive MS (SPMS)
  - Primary progressive MS (PPMS)
  - Progressive/relapsing MS (PRMS)
- Diagnostic criteria for clinically definite MS require documentation of two or more episodes of symptoms and two or more signs that reflect pathology in anatomically noncontiguous white matter tracts of the CNS
- Pregnant MS patients experience fewer attacks than expected during gestation (especially in the last trimester), but more attacks than expected in the first 3 months postpartum.
- Interferon β; glatiramer acetate; mitoxantrone; natalizumab (humanized Ab against α1 subunit of α1β1 integrin) used in treatment

27.ANS A

- Glial cells consist of astrocytes, oligodendrocytes, ependymal cells and microglia.
- Calcification more common in oligodentroglioma

28.ANS E

- Chemotherapy is marginally effective and is often used as an adjuvant therapy following surgery and radiation therapy.
- Temozolomide, an orally administered alkylating agent, has replaced nitrosureas, including carmustine (BCNU) and lomustine (CCNU), as the most widely used chemotherapeutic agent for high-grade gliomas
- WHO 4 tier grading system according to severity
- Pseudo palisading due to necrosis; glomeruloid bodies due to endothelial proliferation seen in glioblastoma
- Gliomatosis cerebri – rare form of astrocytoma in which there is diffuse infiltration of brain. Treated with whole brain radiation

29.ANS E
30.ANS E
31.ANS E
32.ANS D
33.ANS A
34.ANS D

35.ANS D
36.ANS D

- Tuberous sclerosis is characterized by cutaneous lesions, seizures, and mental retardation.
- The cutaneous lesions include adenoma sebaceum (facial angiofibromas), ash leaf–shaped hypopigmented macules (best seen under ultraviolet illumination with a Wood's lamp), shagreen patches (yellowish thickenings of the skin over the lumbosacral region of the back), and depigmented nevi.
- Recognizable by neuroimaging studies, the presence of subependymal nodules, which may be calcified, is characteristic.
- Tuberous sclerosis patients are at increased risk of developing ependymomas and childhood astrocytomas, of which >90% are *subependymal giant cell astrocytomas*

37.ANS D

- This syndrome consists of retinal, cerebellar, and spinal hemangioblastomas, which are slowly growing cystic tumors.
- Hypernephroma, renal cell carcinoma, pheochromocytoma, and benign cysts of the kidneys, pancreas, epididymis, or liver may also occur.
- Erythropoietin produced by hemangioblastomas may result in polycythemia.
- Mutation of the von Hippel–Lindau (*VHL*) gene on chromosome 3p, a tumor-suppressor gene, causes this disorder

38.ANS C

Table 376-2 Cerebrospinal Fluid (CSF) Abnormalities in Bacterial Meningitis	
Opening pressure	>180 mmH_2O
White blood cells	10 to 10,000/μL; neutrophils predominate
Red blood cells	Absent in nontraumatic tap
Glucose	<2.2 mmol/L (<40 mg/dL)
CSF/serum glucose	<0.4
Protein	>0.45 g/L (>45 mg/dL)
Gram's stain	Positive in >60%
Culture	Positive in >80%
Latex agglutination	May be positive in patients with meningitis due to *S. pneumoniae*, *N. meningitidis*, *H. influenzae* type b, *E. coli*, group B streptococci
Limulus lysate	Positive in cases of gram-negative meningitis
PCR	Detects bacterial DNA

- Viral meningitis -The typical profile is a lymphocytic pleocytosis (25–500 cells/μL), a normal or slightly elevated protein concentration [0.2–0.8 g/L (20–80 mg/dL)], a normal glucose concentration, and a normal or mildly elevated opening pressure (100–350 mmH_2O).
- Rarely, PMNs may predominate in the first 48 h of illness, especially with infections due to echovirus 9, eastern equine encephalitis (EEE) virus, or mumps

39.Ans B

- Most important viruses causing sporadic cases of encephalitis in immunocompetent adults are herpesviruses (HSV, VZV, EBV)

40.ANS B

- For cryptococcal meningoencephalitis without a concomitant immunosuppressive condition, the recommended regimen is AmB (0.5–1.0 mg/kg) plus flucytosine (100 mg/kg) daily for 6–10 weeks.
- Alternatively, patients can be treated with AmB (0.5–1.0 mg/kg) plus flucytosine (100 mg/kg) daily for 2 weeks and then with fluconazole (400 mg/d) for at least 10 weeks.

41.ANS D

- Neurocysticercosis is the most common parasitic disease of the CNS worldwide. Humans acquire cysticercosis by the ingestion of food contaminated with the eggs of the parasite *T. solium*
- Albendazole and praziquantel are used in the treatment of neurocysticercosis. Approximately 85% of parenchymal cysts are destroyed by a single course of albendazole, and ~75% are destroyed by a single course of praziquantel.

42.ANS B

- SSPE is a rare chronic, progressive demyelinating disease of the CNS associated with a chronic nonpermissive infection of brain tissue with measles virus.
- Most patients give a history of primary measles infection at an early age (2 years), which is followed after a latent interval of 6–8 years by the development of progressive neurologic disorder.
- Some 85% of patients are between 5 and 15 years old at diagnosis.
- Initial manifestations include poor school performance and mood and personality changes.
- Typical signs of a CNS viral infection, including fever and headache, do not occur.
- As the disease progresses, patients develop progressive intellectual deterioration, focal and/or generalized seizures, myoclonus, ataxia, and visual disturbances.
- MRI is often normal early, although areas of increased T2 signal develop in the white matter of the brain and brainstem as disease progresses.
- The EEG may initially show only nonspecific slowing, but with disease progression, patients develop a characteristic periodic pattern with bursts of high-voltage, sharp, slow waves every 3–8 s, followed by periods of attenuated ("flat") background
- CSF antimeasles antibody levels are invariably elevated, and oligoclonal antimeasles antibodies are often present
- No definitive therapy for SSPE is available

Progressive Multifocal Leukoencephalopathy

- Progressive multifocal leukoencephalopathy (PML) is a progressive disorder characterized pathologically by multifocal areas of demyelination of varying size distributed throughout the brain but sparing the spinal cord and optic nerves
- In addition to demyelination, there are characteristic cytologic alterations in both astrocytes and oligodendrocytes
- Oligodendrocytes have enlarged, densely staining nuclei that contain viral inclusions formed by crystalline arrays of JC virus (JCV) particles.
- Patients often present with visual deficits (45%), typically a homonymous hemianopia; mental impairment (38%) (dementia, confusion, personality change); weakness, including hemi- or monoparesis; and ataxia. Seizures occur in ~20%
- Almost all patients have an underlying immunosuppressive disorder
- The presence of a positive CSF PCR for JCV DNA in association with typical MRI lesions in the appropriate clinical setting is diagnostic of PML

43.ANS D

- Most patients (~90%) with CJD exhibit myoclonus
- Unlike other involuntary movements, myoclonus persists during sleep.
- Startle myoclonus elicited by loud sounds or bright lights is frequent

- Dementia with myoclonus can also be due to Alzheimer's disease , dementia with Lewy bodies , cryptococcal encephalitis , or the myoclonic epilepsy disorder Unverricht-Lundborg disease

44.ANS C

Table 378-2 The Prion Diseases		
Disease	**Host**	**Mechanism of Pathogenesis**
Human		
Kuru	Fore people	Infection through ritualistic cannibalism
iCJD	Humans	Infection from prion-contaminated hGH, dura mater grafts, etc.
vCJD	Humans	Infection from bovine prions
fCJD	Humans	Germ-line mutations in *PRNP*
GSS	Humans	Germ-line mutations in *PRNP*
FFI	Humans	Germ-line mutation in *PRNP* (D178N, M129)
sCJD	Humans	Somatic mutation or spontaneous conversion of PrP^{C} into PrP^{Sc}?
sFI	Humans	Somatic mutation or spontaneous conversion of PrP^{C} into PrP^{Sc}?

Abbreviations: BSE, bovine spongiform encephalopathy; CJD, Creutzfeldt-Jakob disease; fCJD, familial Creutzfeldt-Jakob disease; iCJD, iatrogenic Creutzfeldt-Jakob disease; sCJD, sporadic Creutzfeldt-Jakob disease; vCJD, variant Creutzfeldt-Jakob disease; CWD, chronic wasting disease; FFI, fatal familial insomnia; sFI, sporadic fatal insomnia; FSE, feline spongiform encephalopathy; GSS, Gerstmann-Sträussler-Scheinker disease; hGH, human growth hormone; MBM, meat and bone meal; TME, transmissible mink encephalopathy.

Table 378-1 Glossary of Prion Terminology	
Prion	*Pro*teinaceous *in*fectious particle that lacks nucleic acid. Prions are composed largely, if not entirely, of PrP^{Sc} molecules. They can cause scrapie in sheep and goats, and related neurodegenerative diseases of humans such as Creutzfeldt-Jakob disease (CJD).
PrP^{Sc}	Disease-*c*ausing isoform of the prion protein. This protein is the only identifiable macromolecule in purified preparations of scrapie prions.
PrP^{C}	*C*ellular isoform of the prion protein. PrP^{C} is the precursor of PrP^{Sc}.
PrP 27-30	A fragment of PrP^{Sc}, generated by truncation of the NH_2-terminus by limited digestion with proteinase K. PrP 27-30 retains prion infectivity and polymerizes into amyloid.
PRNP	PrP gene located on human chromosome 20.
Prion rod	An aggregate of prions composed largely of PrP 27-30 molecules. Created by detergent extraction and limited proteolysis of PrP^{Sc}. Morphologically and histochemically indistinguishable from many amyloids.
PrP amyloid	Amyloid containing PrP in the brains of animals or humans with prion disease; often accumulates as plaques.

45.ANS B

Table 380-3 Diagnostic Criteria for Guillain-Barré Syndrome
Required
1. Progressive weakness of 2 or more limbs due to neuropathy[a]
2. Areflexia
3. Disease course <4 weeks
4. Exclusion of other causes [e.g., vasculitis (polyarteritis nodosa, systemic lupus erythematosus, Churg-Strauss syndrome), toxins (organophosphates, lead), botulism, diphtheria, porphyria, localized spinal cord or cauda equina syndrome]
Supportive
1. Relatively symmetric weakness
2. Mild sensory involvement
3. Facial nerve or other cranial nerve involvement
4. Absence of fever
5. Typical CSF profile (acellular, increase in protein level)
6. Electrophysiologic evidence of demyelination

46.ANS C

Table 380-1 Subtypes of Guillain-Barré Syndrome (GBS)			
Subtype	**Features**	**Electrodiagnosis**	**Pathology**
Acute inflammatory demyelinating polyneuropathy (AIDP)	Adults affected more than children; 90% of cases in western world; recovery rapid; anti-GM1 antibodies (<50%)	Demyelinating	First attack on Schwann cell surface; widespread myelin damage, macrophage activation, and lymphocytic infiltration; variable secondary axonal damage
Acute motor axonal neuropathy (AMAN)	Children and young adults; prevalent in China and Mexico; may be seasonal; recovery rapid; anti-GD1a antibodies	Axonal	First attack at motor nodes of Ranvier; macrophage activation, few lymphocytes, frequent periaxonal macrophages; extent of axonal damage highly variable
Acute motor sensory axonal neuropathy (AMSAN)	Mostly adults; uncommon; recovery slow, often incomplete; closely related to AMAN	Axonal	Same as AMAN, but also affects sensory nerves and roots; axonal damage usually severe
M. Fisher syndrome (MFS)	Adults and children; uncommon; ophthalmoplegia, ataxia, and areflexia; anti-GQ1b antibodies (90%)	Demyelinating	Few cases examined; resembles AIDP

47.ANS C

Table 379-2 Classification of Neuropathy by Location	
Polyneuropathy	**Multiple Mononeuropathy**
Fairly symmetric	In distribution of single nerve(s)
Distal stocking-glove	Setting: diabetes, pressure, vasculitis
May or may not be painful	May or may not be painful

Sensorimotor	Isolated reflex loss
Symmetrically decreased reflexes	
Plexopathy	**Not a Neuropathy**
Asymmetric	Upper motor neuron signs (brisk reflexes)
Painful onset	Prominent bladder and bowel involvement
Multiple nerves in a single limb	Unilateral (arm, leg, face) symptoms
Rapid onset of weakness, atrophy	Sensory level
Isolated reflex loss	Hyperventilation

48.ANS A

Small-fiber sensory (painful neuropathies and dissociated sensory loss)
Hereditary sensory neuropathies (early)
Lepromatous leprosy
Diabetic (includes glucose intolerance) small-fiber neuropathy
Amyloidosis
Analphalipoproteinemia (Tangier disease)
Fabry's disease (pain predominates)
Dysautonomia (Riley-Day syndrome)
HIV and antiretroviral therapy neuropathy
Large-fiber sensory (ataxic-neuropathies)
Sjögren's syndrome
Vitamin B12 neuropathy (from dorsal column involvement)
Cisplatin neuropathy
Pyridoxine toxicity
Friedreich's ataxia
Small- and large-fiber: Global sensory loss
Carcinomatous sensory neuropathy
Hereditary sensory neuropathies (recessive and dominant)
Diabetic sensory neuropathy
Vacor intoxication
Xanthomatous neuropathy of primary biliary cirrhosis (tabes dorsalis)

49.ANS B

Motor-predominant neuropathies
Immune neuropathies: acute (Guillain-Barré syndrome); relapsing
Heritable motor-sensory neuropathies
Acute intermittent porphyria
Diphtheritic neuropathy
Lead neuropathy

Brachial neuritis
Diabetic lumbosacralplexus neuropathy (diabetic amyotrophy)
Autonomic
Acute: Acute pandysautonomic neuropathy, botulism, porphyria, GBS, vacore, amiodarone, vincristine
Chronic: Amyloid, diabetes, Sjögren's, HSAN I and III (Riley-Day), Chagas, paraneoplastic

50.ANS C

Table 379-4 Classification of Neuropathy by Histopathology			
	Demyelinating	**Axonal**	**Neuronal**
Pattern	Proximal = distal	Distal > proximal; length-dependent	Non-length-dependent; UE, LE, face
Onset	Acute/subacute	Slow evolution	Rapid
Symptoms	Paresthesia and weakness	Dysesthesias and distal weakness	Paresthesias, gait ataxia
Sensory signs	Vibration and proprioception > pain and temperature	Pain and temperature affected > vibration and proprioception	Vibration and proprioception > pain and temperature
Motor	Distal and proximal weakness	Distal weakness	Proprioceptive weakness
DTRs	Areflexia	Distal areflexia	Areflexia
NCS	Velocity affected > amplitude	Amplitudes affected > velocity	Sensory amplitudes affected; radial > sural
Nerve biopsy	Demyelination and remyelination	Axonal degeneration and regeneration	Axonal degeneration but no regeneration
Prognosis	Rapid recovery	Slow recovery	Poor recovery
Causes	GBS, diphtheria, CIDP, DM, MMN	Toxic, metabolic, HIV, CMT2, DM	Sjögren's, cisplatin, pyridoxine

51.ANS D

52.ANS B

- Descending paralysis - Diphtheria, polio, botulinum

53.ANS A

54.ANS E

- Patients with MuSK antibody–positive MG may not respond to thymectomy.

55.ANS B

56.ANS E

Table 382-5 Progressive Muscular Dystrophies					
Type	**Inheritance**	**Defective Gene/Protein**	**Onset Age**	**Clinical Features**	**Other Organ Systems Involved**
Duchenne	XR	Dystrophin	Before 5 years	Unable to walk after age 12 Progressive kyphoscoliosis Respiratory failure in 2d or 3d decade	Cardiomyopathy Mental impairment

Becker	XR	Dystrophin	Early childhood to adult	Progressive weakness of girdle muscles Able to walk after age 15 Respiratory failure may develop by 4th decade	Cardiomyopathy
Congenital	AR	Several	At birth or within first few months	Hypotonia, contractures, delayed milestones Progression to respiratory failure in some; static course in others	CNS abnormalities (hypomyelination, malformation) Eye abnormalities
Myotonic[a] (DM1, DM2)	AD	DM1: Expansion CTG repeat DM2: Expansion CCTG repeat	Usually 2d decade May be infancy if mother affected (DM1 only)	Slowly progressive weakness of face, shoulder girdle, and foot dorsiflexion Preferential proximal weakness in DM2	Cardiac conduction defects Mental impairment Cataracts Frontal baldness Gonadal atrophy

57.ANS D

58.ANS A
Distal mayopathies

- Welander, Udd, and Markesbery-Griggs distal myopathies are all late-onset, dominantly inherited disorders of distal limb muscles, usually beginning after age 40 years
- Laing distal myopathy is also a dominantly inherited disorder heralded by tibial weakness; however, it is distinguished by onset in childhood or early adult life.
- Nonaka distal myopathy and Miyoshi myopathy are distinguished by autosomal recessive inheritance and onset in the late teens or twenties
- the myofibrillar myopathies (MFM) are a clinically and genetically heterogeneous group of disorders that can be associated with prominent distal weakness; they can be inherited in an autosomal dominant or recessive pattern\

59.ANS E

60.ANS A

- Ocular muscles are spared, even in advanced, untreated cases; if these muscles are affected, the diagnosis of inflammatory myopathy should be questioned

HEMATOLOGICAL MALIGNANCIES

1.Ans.D
Etiology of AML
(1) Heredity
- Chromosomal syndromes – downs, klinfelters, Patau
- Inherited diseases with excessive chromatin fragility – fanconi's anemia, bloom syndrome,AT
Kostmann syndrome -Congenital neutropenia (Kostmann syndrome) is a disease with mutations in the granulocyte colony-stimulating factor (G-CSF) receptor and, often, neutrophil elastase that may evolve into AML
(2) Radiation
(3) Chemicals and drugs
Chemicals-Benzene, smoking, Petroleum products, ethylene oxide
Drugs-Alkylating agents (MC), TopoisomeraseII inhibiters, Chloramphenicol

2.Ans.D
FAB classification – Based on morphology and cytochemistry
M0-Minimally differentiated
- 2 -3%
- Blasts lack definitive cytological and cytochemical markers of myeloblast
Eg:MPO negative

M1- AML without differentiation
- Very immature
- ≥ 3% are peroxidase positive
- Few auer rods seen

M2 – AML with maturation
- 30-40% (MC)
- Auer rods positive in most cases
- often associated with t(8;21) → granulocytic sarcoma

M3-Hyper granular promyelocytic leukemia
- 5 – 10%
- MPO positive

- Many auer rods /cell
- Seen in younger patient
- Associated with t (15;17) → High incidence of DIC
- ATRA , Arsenic used in treatment

M4- Acute myelomonocytic leukemia

- 20%
- Myelocytic and monocytic differentiation
- MPO positive
- Monoblasts positive for NSE
- Subset associated with inv16
- M4 E0 – variant with increase in abnormal marrow eosinophils

M5-Acute monocytic leukemia

- 10%
- Peroxidase negative
- NSE positive
- Older patients
- Higher incidence of organomegaly lymphadenopathy and tissue infiltration like gingival hyperplasia

M6- acute erytholeukemia

- Dysplastic erythroid precussors predominate
- In non erythroid cells >30% are myeloblast
- 20% of therapy related AML

M7- Acute megakaryocytic leukemia

- Blasts of megakaryocytic lineage predominate
- Blasts react with platelet specific antibodies directed against Gp IIb/IIIa and vWF

Table 104-1 Acute Myeloid Leukemia (AML) Classification Systems
World Health Organization Classification[a]
I. AML with recurrent genetic abnormalities AML with t(8;21)(q22;q22);*RUNX1/RUNX1T1*[b] AML with abnormal bone marrow eosinophils [inv(16)(p13q22) or t(16;16)(p13;q22);*CBFB*/*MYH11*][b] Acute promyelocytic leukemia [AML with t(15;17)(q22;q12) (*PML*/*RAR*) and variants][b] AML with 11q23 (*MLL*) abnormalities
II. AML with multilineage dysplasia Following a myelodysplastic syndrome or myelodysplastic syndrome/myeloproliferative disorder Without antecedent myelodysplastic syndrome
III. AML and myelodysplastic syndromes, therapy-related Alkylating agent–related Topoisomerase type II inhibitor–related Other types
IV. AML not otherwise categorized AML minimally differentiated AML without maturation AML with maturation Acute myelomonocytic leukemia Acute monoblastic and monocytic leukemia Acute erythroid leukemia Acute megakaryoblastic leukemia Acute basophilic leukemia Acute panmyelosis with myelofibrosis Myeloid sarcoma

3.Ans.A

Granulocytic sarcoma (chloromas)

- Rarely patients with AML presents with symptoms of mass lesion in soft tissue, breast, uterus, spinal dura, GIT etc…..
- Mass lesion represent a tumor of leukemic cells
- They have green hue due to myeloperoxidase

4.Ans.E

Hematological findings in AML

- Diagnosis - >20% blasts in blood and /or marrow
- Anemia usually present at diagnosis and can be severe
- Median presenting leukocyte count – 15000

- 20% - >1lakh
- 25 – 40% <5000
- <5% - Aleukemic leukemia
  - Platelet count <1lakh in 75% at diagnosis
    - Both morphological and functional platelet abnormality seen

5.Ans.D

Prognostic factors AML

1.Age – most important pretreatment risk factor. Risk increases with age

2.Chromosomal finding

- Good prognosis – t (8;21), inv16, t (15;17) , no cytogenetic abnormality
- Bad prognosis – complex karyotype, inv 3 or -7

3.Anemia leucopenia and thrombocytopenia for > one month duration before diagnosis of AML has poor prognosis.

4.High presenting leukocyte count, relapse, CNS bleeding associated with poor prognosis.

5.Treatment associated secondary leukemia have grave prognosis

6.Expression of MDR-I gene adversely influence outcome

Note: Attainment of CR is most important treatment associated prognostic factor

CR is defined after examination of both blood and bone marrow

-blood neutrophil count >1500 /micro liter
- Platelet count >1Lakh
- Circulating blasts absent
- Bone marrow cellularity >20% with try lineage maturation
- Bone marrow contain <5% blasts and auer rods absent

Note: Hb and hematocrit are not considered in the determining CR

6.Ans.A

Lineage	Antigen
B cell	22, CD9a, cCD79a,
T cell	CD1, CD2, CD3, CD4, CD5, CD7, CD8, cCD3
Lymphoid	TdT
Myeloid	CD13, CD33, CD11b, CD15, CD4, CD117, cMPO
Monocytic	
Erythroid	Glycophorin A
Megakaryocytic	CD41, CD61,
Leukocyte Common antigen	CD45
Stemcell antigen	CD34
CALLA (Common acute Lymphoblastic leukemia antigen)	CD10
Natural killer cells	CD16, CD56

7.Ans.D

High dose cytarabine associated with myelosupression, pulmonary toxicity and irreversible cerebellar toxicity. So patients should be closely monitored for cerebellar toxicity.

Occasionally etoposide is added to increase CR duration.
10% of M3 patient on 7&3 regimen develops DIC due to release of granules by dyeing tumor cells
Tretinoin doesn't produce DIC but it can cause retinoic acid syndrome due to adhesion of tumor cells to pulmonary vascular endothelium which has 10% mortality.
Increased Relapse rate in autogenic graft is due to absence of graft verse leukemia effect and possible contamination of autogenic graft by tumor cells

8.Ans.A
Antibody targeted chemotherapy consisting of humanized anti CD33 antibody linked to calicheamicin, a potent anti tumor antibiotic.
At present used in elderly
Not useful in early relapse or refractory cases
Denileukin diftitox
- Fusion protein used direct diphtheria toxin in it against cells expressing IL-2 receptors
- Used in treatment of mycosis fungoides

Tositumumab
- Iodine 131 linked to anti CD20 antibody used low grade NHL

Ibritumomab tiuxetan
- Ytrium19 targeting CD20 on lymphomas

Table 104-3 Selected New Agents under Study for Treatment of Adults with AML

Class of Drugs	**Example Agent(s)**
MDR1 modulators	Cyclosporine, LY335979
Demethylating agents	Decitabine, 5-azacytidine, zebularine
Histone deacetylase inhibitors	Suberoylanilide hydroxamic acid (SAHA), MS275, LBH589, valproic acid
Heavy metals	Arsenic trioxide, antimony
Farnesyl transferase inhibitors	R115777, SCH66336
FLT3 inhibitors	SU11248, PKC412, MLN518, CHIR-258
HSP-90 antagonists	17-allylaminogeldanamycin (17-AAG) or derivatives
BCR-ABL PDGFR/KIT inhibitors	Imatinib (ST1571, Gleevec), dasatinib, nilotinib
Telomerase inhibitor	GRN163L
Cell cycle inhibitors	Flavopiridol, CYC202 (R-Roscovitine), SNS-032
Nucleoside analogues	Clofarabine, troxacitabine
Humanized antibodies	Anti-CD33 (SGN33), anti-DR4, anti-DR5, anti-KiR
Toxin-conjugated antibodies	Gemtuzumab ozogamicin (Mylotarg)
Radiolabeled antibodies	Yttrium-90-labeled human M195

9.Ans.B
CML
Definition – Clonal expansion of pleuripotent hematopoietic progenitor cells characterized by excessive proliferation of marrow granulocytes, erythroid precussors, megakaryocytes and connective tissue forming cells.
Distinguished form other chronic myelo proliferative disorders by presence of Philadalphia chromosome.
Untreated the disease characterized by inevitable transition from chronic phase to an accelerated phase and on to blast crisis.

Pathogenesis
T (9;22) leads to abl-bcr fusion gene which encodes a chimeric protein that has thyrosine kinase activity, subsequently activating down stream kinases that prevent apoptosis.

Clinical features
90% presents in chronic phase generally insidious
Lethargy weakness, night sweats weight loss are common symptoms

Cytogenetic analysis
Cytogenetic hall mark t(9;22)
Molecular testing – FISH, or RT-PCR for detection of PH chromosome
Note: All patients should have evidence of translocation to make diagnosis of CML

10.Ans.D
Chronic phase
- Increase TLC with various degree of immaturity of granulocyte series
- 5% circulating blasts
- Normotcytic normochormic anemia
- Platelet count almost always increased
- LAP is low in CML
- Serum level of vitamin B12 and B12binding proteins elevated

Bone marrow
Hyper cellular that is 100% cellular (normally 50% cellular 50% fat)
ME ratio 9:1 to 15:1
Marrow blast percentage normal or slightly increased
Characteristic finding – presence of scattered storage histiocyte with wrinkled green blue cytoplasm called Sea blue histiocyte
Increased deposition of reticulin fibres

Accelerated phase
Increase degree of anemia
Blood or marrow blast 10-20%
Blood or marrow basophils ≥ 20%
Platelet count <1lakh

Blast crises
Acute leukemia with blood or marrow blast >20%
Hypo segmented neutrophils may appear (Pleger'-Huet anomaly)
LAP score increase in blast crisis

11.AnsC.
SOKAL INDEX – Based on chemotherapy treated patients
1.Percentage of circulating blasts
2.Spleen size
3.Platelet count
4.Cytogenetic clonal evolution
5.AGE
Haspford system – Based on interferon alpha treated patient
Percentage of eosinophils and basophils used in place of cytogenetic clonal evaluation used in SOKAL index.

12.Ans.A
Imatinib
Competitive inhibition of ATP binding site of Abl kinase
Which leads to inhibition of tyrosine phosphorylation of protein involved in ABL BCR signal transduction.
Imatinib induces apoptosis in cells expressing abl bcr
Patients in chronic phase have rapid response
Myelo suppression is most common hematological side effect
Other drugs are also used for CML

13.Ans.C
Bone marrow aspiration used for myelofibrosis, RBC cell mass for polycythemia and chromosomal evaluation in CMI

14.Ans.C
Juvenile CML

- It is Ph negative and clinically aggressive
- age of onset below 2years
- abrupt onset with eczematoid skin rash, marked lymphadenopathy and bleeding tendency
- chromosomal aberration – monosomy, del 7q
- lab findings – moderate leukocytosis

Thrombocytopenia
Monocytosis
Increased HbF
Normal or decreased ALP
Increased spontaneous growth in cell culture as well as addition of GM-CSF

15.Ans.C

Table 105-4 Infectious Agents Associated with the Development of Lymphoid Malignancies	
Infectious Agent	**Lymphoid Malignancy**
Epstein-Barr virus	Burkitt's lymphoma Post–organ transplant lymphoma Primary CNS diffuse large B cell lymphoma Hodgkin's disease Extranodal NK/T cell lymphoma, nasal type
HTLV-I	Adult T cell leukemia/lymphoma
HIV	Diffuse large B cell lymphoma;Burkitt's lymphoma
Hepatitis C virus	Lymphoplasmacytic lymphoma
Helicobacter pylori	Gastric MALT lymphoma
Human herpesvirus 8	Primary effusion lymphoma Multicentric Castleman's disease

16.Ans.D
Prognostic factors

TABLE 80.2. Prognostic Factors In Acute Lymphoblastic Leukemia

Determinants	Favorable	Unfavorable
White blood cell count	$<10 \times 10^5$/L	$>200 \times 10^5$/L
Age	3–7 yr	<1, >10 yr
Gender	Female	Male
Ethnicity	White	Black
Node, liver, spleen enlargement	Absent	Massive
Testicular enlargement	Absent	Present
Central nervous system leukemia	Absent	Overt (blasts + pleocytosis)
FAB morphologic features	L1	L2
Ploidy	Hyperdiploidy	Hypodiploidy < 45
Cytogenetic markers	Trisomies 4, 10, and/or 17 t(12;21) (tel aml1)	t(9;22) [bcr abl] t(4;11) [mll af4]
Time to remission	<14 d	>28 d
Minimal residual disease	$<10^{-4}$	$>10^{-3}$

17.Ans.A

FAB classification of ALL

Table 105-2 Classification of Acute Lymphoid Leukemia (ALL)			
Immunologic Subtype	**% of Cases**	**FAB Subtype**	**Cytogenetic Abnormalities**
Pre-B ALL	75	L1, L2	t(9;22), t(4;11), t(1;19)
T cell ALL	20	L1, L2	14q11 or 7q34
B cell ALL	5	L3	t(8;14), t(8;22), t(2;8)

L1 – small uniform blast
L2 -larger and more variable size
L3- lymphoid malignancies of uniform cells with basophilia and sometimes vacuolated cytoplasm (typical burkitts lymphoma cell) worst prognosis

18.Ans.B

Treatment of ALL

Induction – oral prednisolone or dexamethasone

- IV vincristine and duanorubicine
- IM asparginase
- Intra thecal methotrexate

Consolidation – cyclo phosphamide, L asparginase
Maintenance- 6MP methotrexate,
Bone marrow transplant is not used as initial treatment
Patients with t(9;22) May have better cure by early BMT

19.Ans.B
CLL and SLL are characterized by accumulation of non proliferating mature appearing lymphocytes in bone marrow, blood, lymph nodes or spleen.
They are similar morphologically phenotypically and genotypically.
Differ only in degree of peripheral blood lymphocytosis (ALC > 4000/mm3)
Most common adult leukemia
Auto immune hemolytic anemia
Molecular Genetics
Deletion 13q
Deletion 11q
Trisomy12
Lab Finding:
Peripheral blood.
Absolute lymphocytosis.
Smudge cells and basket cells seen.
Bone marrow and lymph nodes
Proliferation centers seen
Immuno phenotype
CD19 CD20 CD23 CD5 CD27 positive
CLL may transform to aggressive lymphoma.
Prolymophocytic transformation (15-30 %)
Diffuse large Bcell transformation.(Richter Syndrome-10%)
CD38 , ZAP 70 associated with poor prognosis
No treatment required for asymptomatic patients
Fludrabine DOC in young patients
Chlorambucil DOC in elderly

20.Ans.D
Both MCL and CCL paradoxically positive for CD5 a T-Cell marker
Both positive for pan B-cell marker CD19, CD20, CD22
MCL is CD23 negative

21.Ans.C

Table 105-7 Staging of Typical B Cell Lymphoid Leukemia

Stage	**Clinical Features**	**Median Survival, Years**
RAI System		
0: Low risk	Lymphocytosis only in blood and marrow	>10
I: Intermediate risk	Lymphocytosis + lymphadenopathy + splenomegaly ± hepatomegaly	7
II		
III: High risk	Lymphocytosis + anemia	1.5

IV	Lymphocytosis + thrombocytopenia	
Binet System		
A	Fewer than three areas of clinical lymphadenopathy; no anemia or thrombocytopenia	>10
B	Three or more involved node areas; no anemia or thrombocytopenia	7
C	Hemoglobin 10 g/dL and/or platelets <100,000/ L	2

22.Ans.B
Fludrabine more active agent
Chlorambucil preferred in elderly
Rituximab anti CD20
Alamtizumab –anti CD52

23.Ans.D
Also called L+H cells seen in lympho histocytic variant
Pan B-cell marker CD20 positive
CD15 and CD30 negative which usually shown by other hodgkins cells
Lacunar cells – nodular sclerosis
R-S cells, mononuclear variant –mixed cellular
24.Ans.E

25.Ans.C
Ryes classification
1.Nodular sclerosis
- Most common form 65-75%
- Lacunar cells seen.RS cells rare only form
- Only form more common in females
- Collagen band that divide the lymphoid tissue into circumscribed nodules
- Good prognosis

2.Mixed cellular type
- Most common in India
- Classic RS cells and mononuclear variant predominant
- Associated with older age, B-symptoms, Advanced tumor stage
- Over all good prognosis

3.Lymphocyte predominant type
- Best prognosis long term survival >80%
- L+H Cells common

4.Lymphocyte depletion
- Worst prognosis
- Common in HIV

26.Ans.C

27.Ans.B

Table 105-8 The Ann Arbor Staging System for Hodgkin's Disease	
Stage	**Definition**
I	Involvement of a single lymph node region or lymphoid structure (e.g., spleen, thymus, Waldeyer's ring)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (the mediastinum is a single site; hilar lymph nodes should be considered "lateralized" and, when involved on both sides, constitute stage II disease)
III	Involvement of lymph node regions or lymphoid structures on both sides of the diaphragm

III_1	Subdiaphragmatic involvement limited to spleen, splenic hilar nodes, celiac nodes, or portal nodes
III_2	Subdiaphragmatic involvement includes paraaortic, iliac, or mesenteric nodes plus structures in III_1
IV	Involvement of extranodal site(s) beyond that designated as "E" More than one extranodal deposit at any location Any involvement of liver or bone marrow
A	No symptoms
B	Unexplained weight loss of >10% of the body weight during the 6 months before staging investigation Unexplained, persistent, or recurrent fever with temperatures >38°C during the previous month Recurrent drenching night sweats during the previous month
E	Localized, solitary involvement of extralymphatic tissue, excluding liver and bone marrow

Cost wald staging based on

- CBC ESR
- Serum creatinine
- CXR
- LDH
- CT abdomen, pelvis
- bone marrow biopsy

28.Ans.B

Table 105-3 WHO Classification of Lymphoid Malignancies		
B Cell	**T Cell**	**Hodgkin's Disease**
Precursor B cell neoplasm	Precursor T cell neoplasm	Nodular lymphocyte-predominant Hodgkin's disease
Precursor B lymphoblastic leukemia/lymphoma (precursor B cell acute lymphoblastic leukemia)	**Precursor T lymphoblastic lymphoma/leukemia (precursor T cell acute lymphoblastic leukemia)**	
Mature (peripheral) B cell neoplasms	Mature (peripheral) T cell neoplasms	Classical Hodgkin's disease
B cell chronic lymphocytic leukemia/small lymphocytic lymphoma	T cell prolymphocytic leukemia	Nodular sclerosis Hodgkin's disease
B cell prolymphocytic leukemia	T cell granular lymphocytic leukemia	Lymphocyte-rich classic Hodgkin's disease
Lymphoplasmacytic lymphoma	Aggressive NK cell leukemia	Mixed-cellularity Hodgkin's disease
Splenic marginal zone B cell lymphoma (± villous lymphocytes)	Adult T cell lymphoma/leukemia (HTLV-I+)	Lymphocyte-depletion Hodgkin's disease
Hairy cell leukemia	Extranodal NK/T cell lymphoma, nasal type	
Plasma cell myeloma/plasmacytoma	Enteropathy-type T cell lymphoma	
Extranodal marginal zone B cell lymphoma of MALT type	Hepatosplenic d T cell lymphoma	
Mantle cell lymphoma	Subcutaneous panniculitis-like T cell lymphoma	
Follicular lymphoma	**Mycosis fungoides/Sézary syndrome**	

Nodal marginal zone B cell lymphoma (± monocytoid B cells)	Anaplastic large cell lymphoma, primary cutaneous type	
Diffuse large B cell lymphoma	**Peripheral T cell lymphoma, not otherwise specified (NOS)**	
Burkitt's lymphoma/Burkitt cell leukemia	**Angioimmunoblastic T cell lymphoma**	
	Anaplastic large cell lymphoma, primary systemic type	

29.Ans.D
It is Responsive to chemotherapy. Clinical complete remission occurs with majority of patients and long term disease free survival is frequent.
Hairy cell leukemia

-Rare distinctive B-cell neoplasm
- Males 4:1
- Fine hair like projection from leukemia cells under phase contrast microscope
- Oblong or reineform nucleus
- Histo chemistry and immuno pheno type – TRAP positive neoplastic B-cells
  CD11a, CD19, CD20, CD25, CD103 positive
- Surface immuno globulin positive
- Only NHL infiltrating redpulp
- Clinical features – massive HSM, panatcytopenia
  High incidence of atypical mycobacterium infection
- DOC cladribine
- Usually follow an indolent course

30.Ans.B

31.Ans.D
MALToma

- 8% of NHL
- presents in extra nodal site
- characteristics pattern of infiltration of small lymphocytes that are monoclonal B-cells and CD5 negative
- Can occur in stomach orbit lung, thyroid, CNS, etc…
- Stomach is a most common site
- 95% of gastric MALToma associated with H.pylori and rest t(11:18
- Patients with t(11;18) are genetically stable and do not evolve to diffuse B-cell lymphoma
- Most patients have auto immune or inflammatory process Eg; Sjogrens, hashimotos etc..
- One of the few NHL where surgery is a reasonable primary therapy
- Eradication of H.pylori important
- Very good prognosis

32.Ans.B
Mantle cell lymphoma

- B cell lymphoma, male predominance
- t(11;14) with BCL1 and cyclin D over expression
- CD19, CD20,CD5 positive like CLL but CD23 negative
- Causes lymphomatoid polyposis in colon
- Poor prognosis

33.Ans.C

Table 105-6 Cytogenetic Translocation and Associated Oncogenes Often Seen in Lymphoid Malignancies		
Disease	**Cytogenetic Abnormality**	**Oncogene**
CLL/small lymphocytic lymphoma	t(14;15)(q32;q13)	—
MALT lymphoma	t(11;18)(q21;q21)	API2/MALT, BCL-10
Precursor B cell acute lymphoid leukemia	t(9;22)(q34;q11) or variant t(4;11)(q21;q23)	BCR/ABL AF4, ALLI
Precursor acute lymphoid leukemia	t(9;22) t(1;19) t(17;19) t(5;14)	BCR, ABL E2A, PBX HLF, E2A HOX11L2, CTIP2
Mantle cell lymphoma	t(11;14)(q13;q32)	BCL-1, IgH
Follicular lymphoma	t(14;18)(q32;q21)	BCL-2, IgH
Diffuse large cell lymphoma	t(3;-)(q27;-)[a] t(17;-)(p13;-)	BCL-6 p53
Burkitt's lymphoma, Burkitt's leukemia	t(8;-)(q24;-)[a]	C-MYC
CD30+ Anaplastic large cell lymphoma	t(2;5)(p23;q35)	ALK
Lymphoplasmacytoid lymphoma	t(9;14)(p13;q32)	PAX5, IgH

Follicular Lymphoma

- low grade lymphoma
- Bcell immuno pheno type
- t(14;18) and over expression of BCL2 confirmatory
- DD- reactive follicular hyperplasia
- MC presentation new painless lymphadenopathy
- Most responsible to chemo and radiation
- Single agent chlorambucil or cyclophosphamide
- 25% under go spontaneous regression though transient

34.Ans.D

Diffuse Large B Cell Lymphoma

- most common type of NHL
- dysregulation of BCL2 located on 3q
- CD19, CD20 positive CD5, CD10 variable
- All are TdT negative
- Special subtypes
    1. immuno deficiency associated lymphoma –T cell deficiency
    2. Body cavity large cell lymphoma

35.Ans.B

Burkitts lymphoma

- MC NHL in children
- t(8;14) relatively mature B cells expressing surface IgM
- CD19, CD20, CD10 positive
- Similar to ALL L3
- Starry sky pattern due to tingible macrophages
- MC site of sporadic burkitts – abdomen
- MC site of endemic burkitts – cervical
- Extra nodal most common
- One of the most aggressive tumors but responds well to chemo if given early

36.Ans.A

37.Ans.E
Hallmarks of CTCN – pautrier's micro abscess
- sezary lutzner cell

early cases cured with total skin electron beam radiation
steroids, PUVA, interferon all tried but mainly palliate

38.Ans.C
Working Formulation
1.low grade
- small lymphocytic
- follicular predominantly small cell and mixed

2.Intermediate
- follicular predominantly large cell
- diffuse small cell diffuse large cell
- diffuse mixed cell

3.High grade
- Lymphoblastic
- immuno blastic
- small non cleaved cells

39.Ans.A
Major criteria
1.plasma cytoma on tissue biopsy
2.bone marrow plasma cytosis with >30% plasma cells
3.monoclonal globulin spike on serum electrophoresis or >1gm/24hr light chain excretion on urine electrophoresis in presence of amyloidosis

Minor criteria
1.bone marrow plasma cytosis 10-30%
2.globulin spike <3.5gm/dl for IgG or <2gm/dl for IgA
3.Lytic bonelesions
4.supressed uninvolved immunoglobulin

40.Ans.C
Multiple myeloma
Elderly with raised ESR, anemia with or without increased RFT
Bone pain most common symptom
Vertebra most common site of oesteolytic lesion
No osteoblastic activity hence no increase in ALP and bone scan has no much role.
Metastatic calcification seen
IL6 play important role in plasma cell proliferation
Median age 68
Males more commonly affected
Bone marrow plasma cells are CD138 positive and monoclonal
Serum alkaline phosphatase usually normal because of absence of osteoblastic activity
IgG most common
Patients secreting lamda light chains have poor prognosis
AL amylodosis
Anion gap decreased since M-component is cationic resulting in retention of chloride
Protein cast of urine is made of light chains only
Feiry cells, mot cells and cells containing inclusion bodies seen
cytoplasmic –russels bodies ; nuclear – dutchner bodies
The Durie-Salmon staging system is based on the hemoglobin, calcium, M component, and degree of skeletal involvement
Local radiation for solitary plasmacytoma

Melphalan should be avoided in patients who are candidates for autologous stem cell transplant – VAD regimen (vincristine, adriamycin and dexamethasone)
Thalidomide with dexamethasone equally effective
MPT standard regimen for non transplant pt(melphalan, prednisolone, thalidomide)
Bortezomib (proteasome inhibitor) and lenalidomide are newer agents

41.Ans.C
Calcium levels >50mg/dl associated with poor prognosis
Vigorous hydration is important
IV bisphosphonate like pamidronate is TOC
Steroids, mithramycin, calcitonin also useful in decrease in calcium

42.Ans.C

Table 106-2 Diagnostic Criteria for Multiple Myeloma, Myeloma Variants, and Monoclonal Gammopathy of Unknown Significance
Monoclonal gammopathy of undetermined significance (MGUS)
M protein in serum < 30 g/L
Bone marrow clonal plasma cells < 10%
No evidence of other B cell proliferative disorders
No myeloma-related organ or tissue impairment (no end organ damage, including bone lesions)[a]
Asymptomatic myeloma (smouldering myeloma)
M protein in serum 30 g/L *and/or*
Bone marrow clonal plasma cells 10%
No myeloma-related organ or tissue impairment (no end organ damage, including bone lesions)[a] or symptoms
Symptomatic multiple myeloma
M protein in serum and/or urine
Bone marrow (clonal) plasma cells[b] or plasmacytoma
Myeloma-related organ or tissue impairment (end organ damage, including bone lesions)
Nonsecretory myeloma
No M protein in serum and/or urine with immunofixation
Bone marrow clonal plasmacytosis 10% or plasmacytoma
Myeloma-related organ or tissue impairment (end organ damage, including bone lesions)[a]
Solitary plasmacytoma of bone
No M protein in serum and/or urine[c]
Single area of bone destruction due to clonal plasma cells
Bone marrow not consistent with multiple myeloma
Normal skeletal survey (and MRI of spine and pelvis if done)

No related organ or tissue impairment (no end organ damage other than solitary bone lesion)[a]

43.Ans.D
Walden storms macro globulinemia

- Malignant disease of B cell that appear to be a hybrid of lymphocytes and plasmacells
- Characteristically secretes IgM paraprotein – hyper viscosity
- disease between 60's and 70's
- lymphadenopathy and HSM present
- there is no renal damage
- light chain subtype is kappa in most cases
- fludrabin highly effective single agent

44.ANS C

- (Rituximab) antibody is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes
- It is used in the treatment of B cell NHL (Rituximab)
- in combination with methotrexate is indicated to reduce signs and symptoms in adult patients with moderately- to severely- active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies.
- At the moment it is not licensed for treatment of SLE, but data from case series and phase I and Phase II studies suggest that it is very effective at treating severe SLE and leads to considerable clinical improvement in over 80% of cases. It is usually used in patients that have proved resistant to other therapies.

45. ANS A

46..Ans.C

47. Ans C
Poly neuropathy – progressive sensory motor poly neuropathy
Organomegaly – HSM and lymphadenopathy
Endocrinopathy-Amnorrhea in woman, impotence and gynecomastia in males
Hyper prolactenemia due to loss of inhibition form hypothalamus
Others - Type II diabetis hypothyroidism and adrenal insufficiency
Multiple myeloma
Skin changes - hyper pigmentation, hyper trichosis, skin thickening and digital clubbing
Pathogenesis unclear – increase IL1, IL6
Treatment of myeloma may result in improvement of other symptoms

48.Ans B
PCL. By definition, there are more than 20% plasma cells in the peripheral blood with an absolute plasma cell count of more than 2 × 10 9/L
PCL plasma cells more frequently express the CD20 antigen than those of multiple myeloma, and they often lack CD56 antigen which is present on the majority of myeloma cells

Smoldering multiple myeloma
Serum monoclonal protein (=3 g/dl) or =10% marrow plasma cells or aggregates on biopsy, or both
No anemia, renal failure, or hypercalcemia attributable to myeloma

IgD myeloma accounts for approximately 2% of all cases of myeloma .
The presence of a monoclonal IgD in the serum usually indicates myeloma
Patients with IgD myeloma generally present with a small band or no evident M spike on serum protein electrophoresis
higher incidence of renal insufficiency and coincident amyloidosis, as well as a higher degree of proteinuria than in IgG or IgA myeloma

49.Ans A
The disease is characterized by an infiltration of the lamina propria of the small intestine with lymphoplasmacytoid cells that secrete truncated alpha chains
Gamma Heavy Chain Disease (Franklin's Disease)
Its most distinctive symptom is palatal edema,resulting from node involvement of Waldeyer's ring, and this may progress to produce respiratory compromise.

50.Ans B
There are three categories of structural variation among immunoglobulin molecules that form antigenic determinants, and these are used to classify immunoglobulins
Isotypes are those determinants that distinguish among the main classes of antibodies of a given species and are the same in all normal individuals of that species.
Therefore, isotypic determinants are, by definition, recognized by antibodies from a distinct species (heterologous sera) but not by antibodies from the same species (homologous sera).
There are five heavy chain isotypes (M, G, A, D, E) and two light chain isotypes
Allotypes are distinct determinants that reflect regular small differences between individuals of the same species in the amino acid sequences of otherwise similar immunoglobulins.
These differences are determined by allelic genes; by definition, they are detected by antibodies made in the same species
Idiotypes are the third category of antigenic determinants.
They are unique to the molecules produced by a given clone of antibody-producing cells.
Idiotypes are formed by the unique structure of the antigen-binding portion of the molecule.

HEMATOLOGY PART -II

1. Ans. C ABO
ABO Blood group
- First most important blood group antigen system
- ABO antigens are carbohydrates attached to a precursor backbone made of glycosphingolipids or glycoproteins
- H substances is the immediate precursor up on which A&B antigens are added
- H substances is the formed by addition of fucose to glycolipid or glycoprotein backbone
- Subsequent addition of N asactyl galactosamine creates A antigen while addition of galctose produce B antigen

Bombay phenotype
- Rare individuals lack H gene which codes for fucose transferase and cannot form H substance
- These individuals are homozygous for client H allele and have Bombay phenotype
- These people produce antibodies to H substance (which is present on all red cells except those of hh phenotype) as well as to both A&B antigen and are there for compatible only with hh donors

Genes that determine A&B phenotype located on chromosome 9
Rh gene located on chromosome 1

2. Ans. B

Table 107-1 RBC Blood Group Systems and Alloantigens			
Blood Group System	**Antigen**	**Alloantibody**	**Clinical Significance**
Rh (D, C/c, E/e)	RBC protein	IgG	HTR, HDN
Lewis (Le^a, Le^b)	Oligosaccharide	IgM/IgG	Rare HTR
Kell (K/k)	RBC protein	IgG	HTR, HDN
Duffy (Fy^a/Fy^b)	RBC protein	IgG	HTR, HDN
Kidd (Jk^a/Jk^b)	RBC protein	IgG	HTR (often delayed), HDN (mild)
I/i	Carbohydrate	IgM	None
MNSsU	RBC protein	IgM/IgG	Anti-M rare HDN, anti-S, -s, and -U HDN, HTR

Antibodies to ***Lewis system*** carbohydrate antigens are the most common cause of incompatibility during pretransfusion screening. The Lewis gene product is a fucosyl transferase and maps to chromosome 19. The antigen is not an integral membrane structure but is adsorbed to the RBC membrane from the plasma. Antibodies to Lewis antigens are usually IgM and cannot cross the placenta. Lewis antigens may be adsorbed onto tumor cells and may be targets of therapy

The *P system*. Its clinical significance is in rare cases of syphilis and viral infection that lead to paroxysmal cold hemoglobinuria. In these cases, an unusual autoantibody to P is produced that binds to RBCs in the cold and fixes complement upon warming. Antibodies with these biphasic properties are called *Donath-Landsteiner antibodies*. The P antigen is the cellular receptor of parvovirus B19 and also may be a receptor for *Escherichia coli* binding to urothelial cells

The *Kell* protein. The immunogenicity of Kell is third behind the ABO and Rh systems. The absence of the Kell precursor protein (controlled by a gene on X) is associated with acanthocytosis, shortened RBC survival, and a progressive form of muscular dystrophy that includes cardiac defects. This rare condition is called the *McLeod phenotype*

The *Duffy* antigens are codominant alleles, Fy^a and Fy^b, that also serve as receptors for *Plasmodium vivax*. More than 70% of persons in malaria-endemic areas lack these antigens, probably from selective influences of the infection on the population.

3. Ans. A

4.Ans. E

Table 107-2 Characteristics of Selected Blood Components			
Component	**Volume, mL**	**Content**	**Clinical Response**
PRBC	180–200	RBCs with variable leukocyte content and small amount of plasma	Increase hemoglobin 10 g/L and hematocrit 3%
Platelets	50–70	5.5 x 10^{10}/RD unit	Increase platelet count 5000–10,000/L
	200–400	3.0 x 10^{11}/SDAP product	CCI 10 x 10^9/L within 1 h and 7.5 x 10^9/L within 24 h posttransfusion
FFP	200–250	Plasma proteins—coagulation factors, proteins C and S, antithrombin	Increases coagulation factors about 2%
Cryoprecipitate	10–15	Cold-insoluble plasma proteins, fibrinogen, factor VIII, vWF	Topical fibrin glue, also 80 IU factor VIII

5.Ans.A

FNHTR (Febrile non hemolytic transfusion reaction)

- Most frequent reaction (1-4 : 100)
- Characterized by chills and rigors and >1^{o}C rise in temperature
- Diagnosis of exclusion
- Antibodies directed against donor leukocyte and HLA antigen may mediate these reaction
- Cytokines released from cells within stored blood component may mediate FNHTR
- Leukoreduction before storage may prevent these reaction
- Though antibody can demonstrated, investigation not routinely done because of mild nature of most FNHTR
- Premedication with antipyretics decrease incidents and severity

TRALI (Transfusion related acute lung injury)

- Uncommon reaction due to transfusion of donor plasma that contains high titre of anti HLA antibodies that binds recipient leukocytes
- Leukocytes aggregates in pulmonary vasculature, release mediators and increase permeability
- Patient presents with symptoms of respiratory compromise and signs of noncardiogenic pulmonary edema including bilateral interstitial infiltrate on chest X-ray.
- Treatment supportive and patient usually recovers without sequele
- Testing of donor plasma for anti HLA antibody can support diagnosis
- Implicated donors are frequently multiparous woman and transfusion of their plasma component should be avoided

GVHD

- Frequent complication of allogenic stem cell transplant
- In which lymphocytes form donor attack and cannot be eliminated by an immuno deficient host
- TA-GVHD is mediated by donor T-lymphocytes that recognize host HLA antigen as foreign and mount an immune response
- Manifested clinically by fever, cutaneous eruption, diarrhea and liver function abnormalities
- TAGVHD is characteristically associated with marrow aplasia and pancytopenia
- It is highly resistant to treatment with immuno suppressive therapy
- Clinical features appears at 8-10 days and death occurs at 3-4 weeks host transfusion
- It is prevented by irradiation of cellular component before transfusion to patients at risk and discouraging donation by family members

6. Ans. D

Some gram negative organisms like Yersinia and Pseudomona species can grow at 1-6^{o}C

Platelet concentrate stored at room temperature are more likely to be contaminated

Since blood products contained bradykinia, that normally degraded by ACE, patients on ACE inhibitors have increased bradykinin level that cause hypotension. BP returns normal without intervention.

Hypocalcaemia may follow multiple rapid transfusion. Citrate quickly metabolized to bicarbonate so calcium infusion is rarely required.

Post-transfusion purpura (PTP) is a rare and self-limiting thrombocytopenia occurring 5 to 10 days post transfusion in patients lacking a specific platelet antigen, usually PLA1

The thrombocytopenia can be marked with a platelet count below 10,000/μL. The onset is sudden, although self-limited, and usually resolves in 2 weeks.

Intravenous immunoglobulin (IVIG) appears to be an effective treatment

Although hyperkalemia is often thought to be a problem in massive transfusion, in reality development of hypokalemia is of greater concern.

As the citrate is metabolized to bicarbonate, the blood becomes alkalotic, contributing to hypokalemia.

Transfusion Transmitted Diseases/Infections

* Human Immunodeficiency Virus
* Human T-Lymphotropic Viruses type I and type II
* Hepatitis A
* Hepatitis B
* Hepatitis C

* Hepatitis E
* Hepatitis G virus/GB virus C
* Cytomegalovirus
* Epstein-Barr Virus
* Human Parvovirus B19
* Human Herpesvirus 6
* Human Herpesvirus 8
* TT Virus
* SEN Virus
* CJD and vCJD
* Bacterial Contamination
* Syphilis
* Malaria
* Chagas' Disease
* Toxoplasmosis
* Leishmaniasis
* Babesiosis
* Rocky Mountain Spotted Fever
* Ehrlichiosis

7. Ans. B
Use of peripheral blood stem cells results in more rapid hematopoetic recovery – decreases morbidity of transplantation.
Hematopoetic stem cells circulate in the peripheral blood but in very low concentration
The number of stem cells (identified by expression of CD34 antigen) can be markedly increased by administration of growth factors like GM-CSF and during recovery form intensive chemotherapy.
Umbilical cord blood contains a high concentration of hematopoetic progenitor cells. Lower incidents of GVHD reflect the lesser number of T-cells in cord blood.

8.Ans.E
GVHD
- Result of allogenic T-cells that are either transferred with donor stem cell inoculum or develops from it, reacting with antigenic target on host cells
- GVHD developing in first three months – acute GVHD
- GVHD developing and persisting beyond three months – chronic GVHD

Acute GVHD
- 2 – 4 weeks post transplantation
- Characterized by erethematous maculo papular rash, persistent anorexia or diarrhea or both, by liver disease characterized increased bilirubin, ALT, AST and ALP
- Many conditions mimic acute GVHD, diagnosis by liver, skin or endoscopic biopsy – in all these organs endothelial damage and lymphocytic infiltrates
- Incidents of acute GVHD is higher in

1.Recepients of stem cells from mismatched or unrelated donors
2. In older patients
3. In patients unable to receive full doses of drugs to prevent disease

Prevention
1. Combination of methotrexate + cyclosporine early after transplant – most widely used
2. T-cell depletion – increased incidents of graft failure and tumor recurrence post transplant.

Note
Despite prophylaxis acute GVHD developing 30% of recipient of stem cells from matched siblings and 60% of those from unrelated donors.
Treatment
With steroids, antithymocyte globulin and monoclonal antibody against T-cells

Chronic GVHD

- 20 – 50% of patients surviving >6 months
- Increase incidence with

1. Stem cells mismatched or unrelated donors
2. Older patients
3. History of acute GVHD
   - Disease resemble autoimmune disease – malar rash, sicca syndrome, arthritis, oblitrative bronchiolitis, bile duct degeneration and cholestasis
   - Susceptible to infections. Cotrimoxazole prophylaxis given. Infections treated aggressively
   - Treated with single agent prednisolone or cyclosporine

9.Ans.A
Perpura in HSP is due to vasculitis not thrombocytopenia

TABLE 53-2 Causes of Thrombocytopenia

Decreased marrow production of megakaryocytes
  Marrow infiltration with tumor, fibrosis
  Marrow failure—aplastic, hypoplastic anemias, drug effects
Splenic sequestration of circulating platelets
  Splenic enlargement due to tumor infiltration
  Splenic congestion due to portal hypertension
Increased destruction of circulating platelets
  Nonimmune destruction
    Vascular prostheses, cardiac valves
    Disseminated intravascular coagulation
    Sepsis
    Vasculitis
  Immune destruction
    Autoantibodies to platelet antigens
    Drug-associated antibodies
    Circulating immune complexes (systemic lupus erythematosus, viral agents, bacterial sepsis)

10.Ans.B
ITP caused by immune mediated destruction of platelet and there for platelet supplementation is unlikely to benefit
In ITP specific therapy may not be necessary unless the platelet count is <20000/microL or there is extensive bleeding
Specific therapy include
1.Steroids
2.IV Ig
3.Spleenectomy
4.Immuno suppressive drugs
5.Rituximab
New drugs for ITP include TPO receptor agonists Eltrombopag
This approach to treatment of ITP stems from the finding that many patients with ITP do not have increased TPO levels, as was previously hypothesized, nor do they all have increased platelet destruction. Two agents, one administered subcutaneously and another orally, have shown response in many patients with refractory ITP. Roles for these agents in ITP treatment are not fully defined

11.Ans.C
<u>Chronic ITP</u>

- Woman aged 20-40 years most common
- 3:1 in favor of females
- Prior history of easy bruising or menometorrhagia may be present
- Auto immune disorder with antibody directed against glycoprotein IIb/IIIa or less frequently Gp Ib/IX complex

- Most antibodies function as opsonins and accelerate platelet clearance by phagocyctic cells, occasionally they impair platelet function
- Patients with chronic ITP should have a bonemarrow and ANA done, as low platelet count may be the initial manifestation of SLE or a primary hematological disorder.

12.Ans.C

13.Ans.B

VonWillebrand's disease

- Most common inherited bleeding disorder (1in 100 -500)
- vWF is synthesized by endothelial cells and mega karyocyte
- Normal level 10mg/L
- vWF is a plasma glycoprotein with two major functions
    1. Facilitates platelet adhesion by linking platelet membrane to vascular subendothelium
    2. Serves as plasma carrier for factor 8

3 types of which I and II are autosomal dominant while III is recessive

Investigations

- Prolonged bleeding time
- Reduction in plasma vWF
- Decrease in ristochitin sensitivity
- Decreased factor VIII

Treatment

1.Factor VIII concentration
- It retains HMW vWF multimers
- Recurrent menorrhagia treated with OCPs that suppressed menses

2.Desmopressin
- Increase vWF levels in normal individuals and mild cases
- Type I are the best suited
- Tachyphylaxis can occur the major side effect of DDAVP is hyponatremia due to decreased free water clearance

Antifibrinolytic therapy, using either epsilon-aminocaproic acid or tranexamic acid, is an important therapy, either alone or in an adjunctive capacity, particularly for the prevention or treatment of mucosal bleeding. These agents are particularly useful in prophylaxis for dental procedures, with DDAVP for dental extractions and tonsillectomy, menorrhagia, and prostate procedures. It is contraindicated in the setting of upper urinary tract bleeding, due to the risk of ureteral obstruction

Acquired vWD

- Caused by antibodies that inhibit vWF function or by lymphoid or other tumors that selectively absorb vWF to their surface
- Antibodies – Autoimmune and lymphoproliferative disorders
- Adsorption – Walden storms macroglobulinemia, Wilms tumor
- Heyde's syndrome (aortic stenosis with gastrointestinal bleeding)

14. Ans. A

Bernard soulier syndrome

- Patients have markedly decreased platelet adhesion and cannot bind vWF to their platelet due to deficiency or dysfunction of GP Ib/IX complex
- Also decease levels GpV
- Mild thrombocytopenia
- Extremely large lymphocytoid platelets

Glanzmans thrombasthenia

- Deficient or defect in GpIIb/IIIa complex
- There platelet due not bind fibrinogen and cannot form aggregates
- Platelet normal size

Note

Both are autosomal recessing
Only effective therapy transfusion with normal platelet

15.Ans.C
Hyper tension is not a classical feature of TTP while all others belong to the pentad of symptoms.
TTP
- Fulminant often lethal disorder imitated by endothelial injury and subsequent release of vWF and other procoagulant materials from the endothelial cells
- Presence of severe coombs negative hemolytic anemia with schistocytes or fragmented RBCs in peripheral smear coupled with thrombocytopenia and minimal activation of coagulation cascade.

Pathogenesis
Deficiency in the activity of a specific metalloproteinase called ADAMTS 13 which is responsible for cleaving of UHMW vWF secreted by endothelium to normal multimers present in plasma.
Histology
Hyaline thrombi in arterioles, capillaries, venules with out any inflammatory change in vessal wall diagnostic
Clinical features
Classical PENTAD
1. Hemolytic anemia with fragmented RBC
2. Thrombocytopenia
3. The fuse and non focal neurological deficit
4. Decreased renal function
5. Fever

Treatment
Exchange transfusion or intense plasmapheresis coupled with infusion of FFP

16.Ans.D

17.Ans.B

18. And. D
Hemophilia A
- Factor 8 deficiency
- Gene located on X-chromosome
- Factor 8 synthesized in liver and transported complexed to vWF
- 1 in 10000 males
- Symptomatics have factor 8 < 5%

Lab finding
- Increased aPTT with normal PT, BT and platelet count
- Same with factor 9 deficiency – differentiated by specific assay

19.Ans.D
Factor 13 deficiency
- Classically presents with umbilical bleed and circumcision bleed
- Poor wound healing, infertility among males
- BT, CT and other coagulation test normal
- Clot solubility test with urea and trichloracetic acid positive
- Quantitative chromogen assay more sensitive
- INH mimic factor 13 deficiency by blocking enzyme activity

Factor 9 deficiency (Hemophilia B)
- X-chromosome
- Depended on vitamin K
- Lab findings same as factor 9 deficiency – differentiated by specific assay
- Treatment – FFP
- d by specific assay
- Treatment – FFP

Factor 11 deficiency

- Autosomal recessive
- Ashkenazi jews
- Spontaneous bleeding and hemearthosis rare
- Post surgical bleeding and menorrhagia
- Half life 24 hours – so daily FFA enough

20.Ans.C
Isolated prolongation of aPTT without bleeding manifestation
1.Facotr 12 defect
2. Prekallikrein defect
3. HMW kininogen defect

Table 59-4 Hemostatic Disorders and Coagulation Test Abnormalities
Prolonged activated partial thromboplastin time (aPTT)
No clinical bleeding – factors XII, high-molecular-weight kininogen, protein kinase
Variable, but usually mild, bleeding – factor XI, mild FVIII and FIX
Frequent, severe bleeding – severe deficiencies of FVIII and FIX
Heparin
Prolonged prothrombin time (PT)
Factor VII deficiency
Vitamin K deficiency – early
Warfarin anticoagulation
Prolonged aPTT and PT
Factor II, V or X deficiency
Vitamin K deficiency – late
Direct thrombin inhibitors
Prolonged thrombin time
Heparin or heparin-like inhibitors
Mild or no bleeding – dysfibrinogenemia
Frequent, severe bleeding – afibrinogenemia
Prolonged PT and/or aPTT not correct with mixing with normal plasma
Bleeding – specific factor inhibitor
No symptoms, or clotting and/or pregnancy loss – lupus anticoagulant
Disseminated intravascular coagulation
Heparin or direct thrombin inhibitor
Abnormal clot solubility
Factor XIII deficiency
Inhibitors or defective cross-linking
Rapid clot lysis
Deficiency of $_2$-antiplasmin or plasminogen activator inhibitor 1

Treatment with fibrinolytic therapy

21.Ans.B

Vitamin K deficiency

- Factor 2,7, 9, and 10 ; protein C&S effected
- Factor 7 and protein C decreased first since they have minimum half life
- So initially PT prolonged normal PTT
- Later both prolonged
- Treatment – Parenteral 10.mg vitamin K

  Severe hemorrhage – FFP

22. Ans.A

Table 59-3 Risk Factors for Thrombosis	
Venous	**Venous and Arterial**
Inherited	Inherited
Factor V Leiden	Homocystinuria
Prothrombin G20210A	Dysfibrinogenemia
Antithrombin deficiency	
Protein C deficiency	Mixed (Inherited and acquired)
Protein S deficiency	Hyperhomocysteinemia
Elevated FVIII	
	Acquired
Acquired	Malignancy
Age	Antiphospholipid antibody syndrome
Previous thrombosis	Hormonal therapy
Immobilization	Polycythemia vera
Major surgery	Essential thrombocythemia
Pregnancy & puerperium	Paroxysmal nocturnal hemoglobinuria
Hospitalization	Thrombotic thrombocytopenic purpura
Obesity	Heparin-induced thrombocytopenia
Infection	Disseminated intravascular coagulation
APC resistance, nongenetic	
Unknown[a]	
Elevated factor II, IX, XI	
Elevated TAFI levels	
Low levels of TFPI	

- Hyperhomocysteinemia may be both a genetic and acquired abnormality.
- The most common genetic defect is homozygosity for a thermolabile mutant of the enzyme methylenetetrahydrofolate reductase (MTHFR).
- Plasma homocysteine concentrations can also be increased by deficiencies in vitamin B6, B12, or folic acid.

- Homocysteine is an independent risk factor for atherosclerotic vascular disease, with the risk increasing in a graded fashion with increasing plasma homocysteine concentrations.
- Hyperhomocysteinemia has been associated with an increased risk for VTE

23.Ans.A

Anticoagulation

1. Antithrombin III
   Binds to IX a, Xa, XIa, XIIa and inactivate them in presence of heparin
2. Protein C & S
   Inactivate factor Va and VIIIa
   Also inactivate inhibitor of tissue plasminogen activator
3. Thrombomodulin
   Binds to thrombin and activates protein C

Factor V leaden

- Single point mutation in factor V
- which makes the molecule resistant to degradation by activated protein C
- Responsible for 25% of recurrent DVT and PE
- Absent Asians
- 3% of population world wide hetrozygote for this mutation
- Homozygote have 20 fold increase risk of thrombosis

24.Ans.E

25.Ans.B

Ticlopidine is thienopyridine like clopidogrel and selectively inhibit ADP induced platelet aggregation use a decease due to hematological toxicities including TTPSide Effects

In addition to bleeding, thrombocytopenia is the most serious complication. Thrombocytopenia is immune-mediated and is caused by antibodies directed against neoantigens on GPIIb/IIIa that are exposed upon antagonist binding. With abciximab, thrombocytopenia occurs in up to 5% of patients. Thrombocytopenia is severe in ~1% of these individuals. Thrombocytopenia is less common with the other two agents, occurring in ~1% of patients.

Indications

Abciximab and eptifibatide are used in patients undergoing percutaneous coronary interventions, particularly those with acute MI. Tirofiban is used in high-risk patients with unstable angina. Eptifibatide also can be used for this indication.

26.Ans.E

True heparin resistance – due to nonspecific heparin binding to WBC, vascular endothelial cells and acute phase proteins.

Result in inadequate anticoagulant effect

Apparent heparin resistance - as a result of elevated factor VIII level

MOA

Heparin binds to antithrombin via its pentasaccharide sequence. This induces a conformational change in the reactive center loop of antithrombin that accelerates its interaction with factor Xa. To potentiate thrombin inhibition, heparin must simultaneously bind to antithrombin and thrombin. Only heparin chains composed of at least 18 saccharide units, which correspond to a molecular weight of 5400, are of sufficient length to perform this bridging function. With a mean molecular weight of 15,000, all of the heparin chains are long enough to do this.

B. LMWH has greater capacity to potentiate factor Xa inhibition by antithrombin than thrombin because, with a mean molecular weight of 4500–5000, at least half of the LMWH chains are too short to bridge antithrombin to thrombin.

C. The pentasaccharide only accelerates factor Xa inhibition by antithrombin because the pentasaccharide is too short to bridge antithrombin to thrombin.

27.Ans.D

LMWH is only partially neutralized (60%) by protamine sulfate

LMWH

Derived from enzymatic or chemically cleavage of UFH in to a mixture of glycosaminoglycans with a mean molecular mass of 5KDa (= 15 saccharide unit)
Due to predominance of molecule <18 saccharide, LMWH has limited antithrombin activity compared to anti factor Xa activity (4:1)

28. Ans.D
HIT
- Platelet count <100000 or 50% less than prior to treatment
- 3% patients in 5-10 days after treatment
- Low incidents LMWH
- Thrombotic complication may precede development of HIT
- Due to development of IgG antibody against complexes of heparin and platelet
- Treatment – immediate stoppage of drug other anticoagulants to be started to prevent thrombotic complication
- Argatroban current DOC
- Warfarin should not be started until platelet count comes back to normal or it may cause venous limb Gangrene

29.Ans.A
Fondaparinux
- Synthetic pentasaccharade that causes selective indirect inhibition of factor Xa
- No therapeutic monitoring required
- Less incidence of HIT
- Idraparinux – long acting pentasaccharade

Weakly once dosage
Lepirudin
- Recombinant hirudin which is potent irreversible DTI
- Lack of antidote is the challenge

Argatroban
- Reversible DTI
- Current DOC for HIT

Ximelagatran- Oral prodrug of DTI melagatran
Bivalirudin – reversible DTI with very short half life

30.Ans.B
Myeloproliferative disorders classically include
- Polycythemia vera
- Idiopathic myelo fibrosis
- Essential thrombocytosis
- CML

31. Ans.D

32.Ans.D
High altitude associated with absolute polycythemia not relative

Table 103-2 Causes of Erythrocytosis
Relative erythrocytosis: Hemoconcentration secondary to dehydration, androgens, or tobacco abuse **Absolute erythrocytosis** *Hypoxia* Carbon monoxide intoxication High affinity hemoglobin High altitude Pulmonary disease

Right-to-left shunts
Sleep-apnea syndrome
Neurologic disease
Renal disease
Renal artery stenosis
Focal sclerosing or membranous glomerulonephritis
Renal transplantation
Tumors
Hypernephroma
Hepatoma
Cerebellar hemangioblastoma
Uterine fibromyoma
Adrenal tumors
Meningioma
Pheochromocytoma
Drugs
Androgens
Recombinant erythropoietin
Familial (with normal hemoglobin function, Chuvash, erythropoietin receptor mutations)
Polycythemia vera

33.Ans.A
Alkylating agents are leukemogenic in polycythemia vera and their use should be avoided
Anagrelide – platelet antiaggregant that also lowers platelet count and can control thrombocytosis

34.Ans.C

35.Ans.C

TABLE 95-5 Suggested Criteria for the Clinical Diagnosis of Essential Thrombocytosis[a]

Platelet count ≥ 500,000/μL
Absence of a known cause of reactive thrombocytosis (see Table 95-4)
Absence of the Ph chromosome and the bcr-abl gene rearrangement
Normal red cell mass
Presence of marrow iron
Absence of myelofibrosis
Absence of myelodysplasia clinically and by cytogenetic analysis
Splenomegaly

36.Ans.D

Secondary granules do not contain acid hydrolases and therefore are not classic lysosomes
Primary granules appear in promyelocyte stage and contain

- Hydrolases
- Elastase
- Myeloperoxidase
- Cathepsin G
- Cationic protein
- Permeability increasing protein
- Defensins

Secondary granules appear in myelocyte stage

- Lacto ferrin
- Vitamin B12 binding protein
- Membrane component of NADPH
- Histaminase
- Receptors for laminin

37.Ans.E
Absolute neutrophil count = neutrophil + bandform
Dohle bodies

- Are cytoplasmic inclusion seen in acute infection and are fragments of ribosome rich ER

Toxic granulations

- Prominent neutrophil cytoplasmic granules seen in acute infection

38.Ans.C
WG causes neutropenia

Table 61-1 Causes of Neutropenia
Decreased Production Drug-induced—alkylating agents (nitrogen mustard, busulfan, chlorambucil, cyclophosphamide); antimetabolites (methotrexate, 6-mercaptopurine, 5-flucytosine); noncytotoxic agents [antibiotics (chloramphenicol, penicillins, sulfonamides), phenothiazines, tranquilizers (meprobamate), anticonvulsants (carbamazepine), antipsychotics (clozapine), certain diuretics, anti-inflammatory agents, antithyroid drugs, many others] Hematologic diseases—idiopathic, cyclic neutropenia, Chédiak-Higashi syndrome, aplastic anemia, infantile genetic disorders (see text) Tumor invasion, myelofibrosis Nutritional deficiency—vitamin B_{12}, folate (especially alcoholics) Infection—tuberculosis, typhoid fever, brucellosis, tularemia, measles, infectious mononucleosis, malaria, viral hepatitis, leishmaniasis, AIDS **Peripheral Destruction** Antineutrophil antibodies and/or splenic or lung trapping Autoimmune disorders—Felty's syndrome, rheumatoid arthritis, lupus erythematosus Drugs as haptens—aminopyrine, -methyldopa, phenylbutazone, mercurial diuretics, some phenothiazines Wegener's granulomatosis **Peripheral Pooling (Transient Neutropenia)** Overwhelming bacterial infection (acute endotoxemia) Hemodialysis Cardiopulmonary bypass

39.Ans.D

Table 61-4 Inherited Disorders of Phagocyte Function: Differential Features		
Clinical Manifestations	**Cellular or Molecular Defects**	**Diagnosis**
Chronic Granulomatous Diseases (70% X-linked, 30% Autosomal Recessive)		
Severe infections of skin, ears, lungs, liver, and bone with catalase-positive microorganisms such as *S. aureus*, *Burkholderia cepacia* , *Aspergillus* spp., *Chromobacterium violaceum* ; often hard to culture organism; excessive	No respiratory burst due to the lack of one of four NADPH oxidase subunits in neutrophils, monocytes, and eosinophils	NBT or DHR test; no superoxide and H_2O_2 production by neutrophils; immunoblot for NADPH oxidase components; genetic

inflammation with granulomas, frequent lymph node suppuration; granulomas can obstruct GI or GU tracts; gingivitis, aphthous ulcers, seborrheic dermatitis		detection
Chédiak-Higashi Syndrome (Autosomal Recessive)		
Recurrent pyogenic infections, especially with *S. aureus*; many patients get lymphoma-like illness during adolescence; periodontal disease; partial oculocutaneous albinism, nystagmus, progressive peripheral neuropathy, mental retardation in some patients	Reduced chemotaxis and phagolysosome fusion, increased respiratory burst activity, defective egress from marrow, abnormal skin window; defect in LYST	Giant primary granules in neutrophils and other granule-bearing cells (Wright's stain); genetic detection
Specific Granule Deficiency (Autosomal Recessive)		
Recurrent infections of skin, ears, and sinopulmonary tract; delayed wound healing; decreased inflammation; bleeding diathesis	Abnormal chemotaxis, impaired respiratory burst and bacterial killing, failure to upregulate chemotactic and adhesion receptors with stimulation, defect in transcription of granule proteins; defect in C/EBP	Lack of secondary (specific) granules in neutrophils (Wright's stain), no neutrophil-specific granule contents (i.e., lactoferrin), no defensins, platelet granule abnormality; genetic detection
Myeloperoxidase Deficiency (Autosomal Recessive)		
Clinically normal except in patients with underlying disease such as diabetes mellitus; then candidiasis or other fungal infections	No myeloperoxidase due to pre- and posttranslational defects	No peroxidase in neutrophils; genetic detection
Leukocyte Adhesion Deficiency		
Type 1: Delayed separation of umbilical cord, sustained neutrophilia, recurrent infections of skin and mucosa, gingivitis, periodontal disease	Impaired phagocyte adherence, aggregation, spreading, chemotaxis, phagocytosis of C3bi-coated particles; defective production of CD18 subunit common to leukocyte integrins	Reduced phagocyte surface expression of the CD18-containing integrins with monoclonal antibodies against LFA-1 (CD18/CD11a), Mac-1 or CR3 (CD18/CD11b), p150,95 (CD18/CD11c); genetic detection
Type 2: Mental retardation, short stature, Bombay (hh) blood phenotype, recurrent infections, neutrophilia	Impaired phagocyte rolling along endothelium	Reduced phagocyte surface expression of Sialyl-Lewis^x, with monoclonal antibodies against CD15s; genetic detection

40.Ans.A
Used in treatment of rheumatoid arthritis, chorines disease
Adverse effect –associated with severe infections like TB

TRAPS (TNF alpha Receptor Associated Periodic Syndrome)

- Recurrent fever in the absents of infection
- Due to mutation increasing TNF alpha activity

41.Ans.B
Eosinopenia occurs with stress such as acute bacterial infection and after treatment with steroids
It associate with no adverse effect

In eosinophillia tissue damage is by local deposition of toxic eosinophill protein like cationic protein and major basic protein
In heart pathological changes lead to thrombosis, endocardial fibrosis and restrictive cardiomayopathy.

42.Ans A

43.Ans

44. Ans A

45. Ans A

ANEMIAS

1.Ans.D
Causes of microcytic hypochromic anemias
1.Iron deficiency anemia
2.Thalassemia
3.Sidroblastic anemia
4.Anemia of chronic disease
Fanconi's anemia causes aplastic anemia with normocytic normochromic picture
Fanconi's anemia, an autosomal recessive disorder, manifests as congenital developmental anomalies, progressive pancytopenia, and an increased risk of malignancy.
Chromosomes in Fanconi's anemia are peculiarly susceptible to DNA cross-linking agents, the basis for a diagnostic assay.
Patients with Fanconi's anemia typically have short stature, café au lait spots, and anomalies involving the thumb, radius, and genitourinary tract.

2. Ans.A
Serum iron
Represent amount of circulating iron bound to transferrin.
Normal ranges 50 to 150 micro gram/dl
Decreased iron deficiency anemia (<30), anemia of chronic disease (<50)
Normal to High in thalassemia and sideroblastic anemia

TIBC
Indirect measure of circulating transferrin
Normal value 300 – 360 micro gm /dl

>360 in iron deficiency anemia,
Decreased in chronic disease
Normal in thalassemia and sideroblastic anemia

Transferrin saturation
Serum iron x 100
TIBC
Normal 25 – 50 %
Iron deficiency anemia it is below 18%
Low in chronic disease
High in thalassemia and sideroblastic anemia

Serum ferritin
With in cell iron is stored complexed to proteins as ferritin or hemosiderin
Apoferritin binds to ferrous iron and stores it in ferric state
Serum ferritin is the best test to estimate iron stores
Normal value 30-200 micro gram /l
In iron deficiency anemia ≤15 micro gram/l
Normal are increased in others

Normal values
HbA_2 1.5 – 3.5% of total Hb
HbF >2% of total Hb

Note:
Hypochoromic microcytic anemia with decreased serum iron and increased TIBC – Iron deficiency anemia
Hypochoromic microcytic anemia with decreased serum iron and decreased TIBC – anemia of chronic disease.

Diagnosis of Microcytic anemias

Test	Iron deficiency	Inflammation	Thalassemia	Sideroblastic
Smear	Microcytic Hypochromic	Normal/MIcrocytic Hypochromic	Microcytic Hypochromic	Variable
Serum iron	<30	<50	Normal/High	Normal –High
TIBC	>360	<300	Normal	Normal
% saturation	<10	10-20	30-80	30-80
Ferritin	<15	30-200	50-300	50-300
Hb pattern	Normal	Normal	Abnormal	Normal

The Mentzer index is used to differentiate iron deficiency anemia from beta thalassemia
It is calculated from the results of a complete blood count. If the quotient of the mean corpuscular volume divided by the red blood cell count is less than 13, thalassemia is more likely. If the result is greater than 13, then iron-deficiency anemia is more likely

3.Ans.B
Iron absorption
Duodenum primary site of absorption
Heme iron enters mucosal cells directly
Non heme iron first converted to ferrous
Transported outside cell through baso lateral membrane with the help of transporter called FERRIPORTIN
It is converted to ferric form with the help of HEPHAESTIN and trasported with transferrin
Specific transferrin receptor on the surface of cells of many tissue but highest on marrow erythroid
Excess iron stored as FERRITIN attached to apoferritin.
Stages of iron deficiency
1.Negative iron balance

Demand for iron exceeds body ability to absorb iron form diet
Red cell morphology and indices normal
Only Change – decrease serum ferritin
2.Iron deficient erythropoesis
Iron stores become depleted and serum iron begins to fall
Peripheral smear shows first appearance of microcytic cell

3.Iron deficiency anemia
Gradually Hb and Hematocrit begins to fall
Note:
When moderate anemia is present the bone marrow is hypoproliferative. With more severe and prolonged anemia the erythroid marrow becomes increasingly ineffective resulting in marrow hyperplasia rather than hypoproliferation

Cardinal rule
Appearance of iron deficiency anemia in an adult male means GIT blood loss unless otherwise proved.

4.Ans.C

5.Ans.A
Level of anemia correlates with severity of renal failure in CRF
In ARF the correlation may be weaker
In HUS increase erythropoietin due to hemolysis
PCOD shows only a small degree of erythropoietin deficiency for the given level of renal failure

6.Ans.C
Anemia of chronic disease
Most important DD of iron deficiency
Due to inadequate iron delivery to marrow despite presence of normal or increased iron stored.
Reflected by – low serum iron
Increased red cell protoporphyrin
Hypoproliferative marrow
Transferrin saturation 15-20%
normal or increased serum ferritin (about 3 fold)

Pathogenesis
Due to effect of inflammatory cytokines and hepcidin
IL1 – directly decrease erythropoietin production
IFN gamma and TNF alpha – suppresses the response to erythropoietin
Hepcidin
A liver derived polypeptide blocks
Blocks duodenal iron uptake by inhibiting ferriportin activity
Also suppresses iron release form storage site.

Primary disease will determine the severity and characteristic of anemia Eg:
Cancer – Normocytic normochromic
TB,RA-Microcytic hypochromic

7.Ans.D
Red cell first appear at about 6 weeks after conception
Contains embryonic Hb –Hb Protland, Hb gower1 and gower2
At 10 to 11weeks HbF becomes predominant
Switch to exclusive synthesis of adult Hb (HbA) occurs at 38 weeks
Small amount of HbF are produced during postnatal life by immature committed elytroid precussors
HbF production is increased in severe hemolytic anemias after bone marrow transplant or during chemotherapy.
This HbF is increased in some sickle cell anemia and thalassemia patients
Hydroxurea increase HbF by same mechanism

Fetal Hb can be activated partially after birth by agents such as butyrate which inhibit histone de acetylase and modified structure of chromatic

8.Ans.A
SS x AA

	S	S
A	AS	AS
A	AS	AS

SS Sickle cell disease
AA Normal
AS Sickle Cell trait

9.Ans.D
Microcyotsis occurs in all thalassemia except silent alpha thalassemia carrier state in which only one of the four alpha globin gene is deleted. They have no hematological abnormality.
Patient with two of the four gene deleted (alpha thalassemia trait) Have microcytic and slightly hypochromic red cells without significant hemolysis or anemia. Hb electrophoresis may be normal or with decreased HbA_2
Deletion of Three of the four alpha gene, so call Hemoglobin H disease which is associated with production of HbH (Beta chain Tetramer) on Hb electrophoresis.
There are only two genes for beta thalassemia. Patient with mutation on one gene will have microcytosis abnormal red cells and elevated HbA_2 and HbF in serum electrophoresis.
Any patient with at least one allele with HbS mutation will demonstrate sickling under decreased oxygen tension (Na Metabisulphate test)
Patient with HbE disease have abnormal Hb electrophoresis slightly macrocytic red cells and target cells but no anemia or other clinical manifestation.

10.Ans.A
<u>Pain full crisis</u>
Intermittent episodes of vaso-occlusion in connective tissue and musculo skeletal system produce painful ischemia manifested as acute pain tenderness tachycardia anxiety and fever. It is most common clinical manifestation.
Granulocytosis is common
Spleen lost in 18-36 months
Isosthenuria and painless hematuria due to renal papillary necrosis.
Other symptoms include hand foot syndrome and acute chest syndrome

<u>Clinical Manifestation of sickle cell trait</u>
Usually asymptomatic
Though uncommon painless hematuria is a distinctive symptom
Isosthinuria is a more common manifestation

11.Ans.D
Action of hydroxurea
1.Increases HbF
2.Benificial is effect on red cell hydration
3.Surprssion of granulocyte and reticulocyte count
4.anit inflammatory agent
5.Increase red cell volume
6.Increase NO production

<u>Other drugs</u>
5-deoxy azacytadine (decitabine) – Increase HbF with acceptable toxicity
Adjuvants clotrimazole, magnesium

<u>Definitive cure</u>

Bone marrow early childhood

12.Ans.A
There are no Beta chain in sickle cell disease hence no HbA ($\alpha_2 \beta_2$)
In hetrozygotes (trait) 40% of beta chain defective (HbS)
In Homozygotes (disease) 100% Beta chain defective
HbA_2 and HbF have not beta chain so they will be found normally

13.Ans.A
Both A & B are responsible for beta thalassemia but aberrant splicing is most common
Both are caused by point mutations mainly
Alpha thalassemia is caused by deletion of alpha globulin gene

14.Ans.B
Adult hemoglobin, or HbA, is a tetramer composed of two α chains and two β chains.
The α chains are encoded by two α-globin genes, which lie in tandem on chromosome 16, while the β chains are encoded by a single β-globin gene located on chromosome 11.
The β-globin mutations associated with β-thalassemia fall into two categories: (1) β^0, in which no β-globin chains are produced; and (2) β^+, in which there is reduced (but detectable)
β-globin synthesis inheriting one abnormal allele have *thalassemia minor* or *thalassemia trait,* which is asymptomatic or mildly symptomatic.
Most individuals inheriting any two β^0 and β^+ alleles have β-thalassemia major; occasionally, individuals inheriting two β^+ alleles have a milder disease termed β-thalassemia intermedia
Thalassemia intermedia
Presence of pallor and HSM without need for blood transfusion suggest it

Thalassemia major
Manifest 3-9 months after birth when HbF disappears
Hb 3-6 gm /dl
Transfusion depended
Reticulocyte elevated
HbF markedly increased
HbA_2 may be normal low or High (1.5 – 4%)

15.Ans.D
Thalassemia minor
Offers resistance against plasmodium falciparum
HbA_2 4 – 8% characteristic
HbA 90-93%
Mild anemia Reticulocyte count normal
MCV and MCH decreased
Recognition important because
To differentiate from iron deficiency anemia
For genetic counseling

Screening – NESTROFT
Confirmation – Serum electrophoresis

16.Ans.B
Vitamin C should not supplemented because it generate free radicals in iron excess state

17.Ans.D

18.Ans.B

Causes of macrocytic anemia
1.Vitamin B_{12} deficiency
2.Folic acid deficiency
3.Orotic aciduria
4.Nitrous oxide inhalation
5.Liver disease
6.Hypothyrodism
7.Thiamine

Gene for folate carrier located on chromosome 21
Solute carrier family 19 (folate transporter), member 1, also known as SLC19A1 or RFC1, is a protein which in humans is encoded by the SLC19A1 gene

19.Ans.B
The IF-cobalamin complex passes to the ileum, where IF attaches to a specific receptor (cubilin) on the microvillus membrane of the enterocytes.
Cobalamin appears in portal blood attached to transcobalamin (TC) II

20.Ans.C
H pylori as no roll in parital cell destruction
90% have anti parital antibodies directed against H+ - K+ ATPase
60% have anti intrinsic factor antibodies
Hyper gastrinemia is seen
Increase risk of gastric polyp and Ca-stomach

21.Ans.A
Competition by the worm for cobalamine
Destruction of worm eliminate the problem

22.Ans.B
Causes thiamine deficiency
Mal nutrition
Dietary habits
Alcoholism
CHF patients on diuretic

23.Ans.A
It associated with low Reticulocyte count
Fenestrated pattern of nuclear chromatin is characteristic
In effective erythropoiesis

24.Ans.D
Thalassemia extra vascular hemolysis

Difference between extra vascular and intra vascular hymolysis
1.Absence of hemoglobinemia and hemoglobinuria in extra vascular
2.Decrease in Haptoglobulin is less in extra vascular compared to intra though it decreases in both

25.Ans.D
High Reticulocyte count seen in
1.Hemolysis
2.Bleeding

Low Reticulocyte count
Iron deficiency anemia
Thalassemia

Anemia of chronic disease
Marrow failure Eg:Aplastic anemia

26.Ans.B
About 50% of patients have defects in ankyrin
25% have defects in spectrin and protein 3 (anion transport channel) respectively
Rarely due to mutation of protein 4.2 (palledan)

27.Ans.C
Hereditary spherocytosis
Autosomal dominant
Life span of spherocytes-10-20 days
Normal or decreased MCV but increased MCHC so spherocytes small cells without central pallor
Aplastic crisis by parvo virus infection
Osmotic fragility increased
Anemia splenomegaly and jaundice seen
May present at birth but usually late

28.Ans.B
Splenectomy recommended in patients with moderate or severe hemolysis
RBC survival becomes normal
Cholecystectomy should not be perform without splenectomy as intrahepatic gall stones may result
Splenectomy is usually postponed until age four if possible

29.Ans.D
Due to the action of Phospholipase on membrane

30.Ans.A
Viral and bacterial infections are most common cause
Sulfonamides most common drugs?

31.Ans.B
Oxidation of Hb leads to Heinz bodies
Visualized by supravital stains such as crystal violet
Seen only for one day after that removed by spleen resulting in bite cells
Missense mutation lead to misfolding of G6PD protein

32.Ans.C

Table 101-1 Classification of Hemolytic Anemias[a]

	Intracorpuscular Defects	**Extracorpuscular Factors**
Hereditary	Hemoglobinopathies	Familial hemolytic uremic syndrome (HUS)
	Enzymopathies	
	Membrane-cytoskeletal defects	
Acquired	Paroxysmal nocturnal hemoglobinuria (PNH)	Mechanical destruction (microangiopathic)
		Toxic agents
		Drugs
		Infectious
		Autoimmune

33.Ans.D
Autoimmune hemolytic anemia

Direct coombs test positive
Splenomegaly positive

Warm antibody type
IgG meditated mostly
At 37^{o} C
Etiology
Primary – 60% idiopathic
Secondary
1. Lymphoma & Leukemia (CLL)
2. SLE & other collagen vascular disease
3. Drugs
    Direct anti body model – alpha methyl dopa
    Hapten model – Penicillin, quinidine
4.Post viral infection
5.Other tumors (rare)

Cold antibody type
IgM mediated
Invitro active at 0-4^{o}C
In body below 30^{o}C
Etiology
    Acute – IMN, M pneumonia
    Chronic – Idiopathic, lymphomas
    Paroxysmal cold hemoglobinuria

34.Ans.C

35.Ans.A
All other are autoimmune conditions

36.Ans.B
PNH
Acquired intrinsic defect in cell membrane
Acquired mutation in PIGA gene which is essential for synthesis of GPI anchor
The GPI linked protein activity decrease
    1.CD55 (decay accelerating factor) – most important
    2. CD59 (membrane inactivator of reactive lysis)
    3.C8 binding protein

CD55 is a potent inactivator of C3 convertase and there by prevent spontaneous activation of alternate complement pathway invivo.
This result in unusual sensitivity of RBC to be lysed by compliment
Note-defect not limited to RBC. platelet and granulocytes are also prone to lysis

C/F – Typical PNH in only 25%
Chronic hemolysis with out hemoglobinuria is more common
Episodic venous thrombosis since compliment stimulates platelet aggregation
Increase risk of development of AML
Investigation
Increased LDH and decreased LAP
Ham test positive
Sucrose lyses test positive
Best – Analysis of GPI linked protein by flow cytometry
Treatment
Transfusion Therapy, steroids

Heparin therapy for thrombosis
Humanized monoclonal antibody, **eculizumab**, directed against the complement protein C5 . By blocking the complement cascade downstream of C5, this antibody provides a medical intervention capable of controlling complement-dependent hemolysis in PNH

37.Ans.C

38.Ans.D

39.Ans.D
PCH & cold hemolytic anemia respond poorly to splenectomy
Warm antibodies respond well
Chronic PCH respond well to prednisone and cytotoxic therapy
Evan's syndrome- Immune Hemolytic anemia + immune thrombocytopenia

40.Ans.A
Hemolytic anemia with bezzare shaped RBC in 5% patients with severe hepato cellular disease

41.Ans.D

Table 102-2 Classification of Aplastic Anemia	
Acquired	**Inherited**
Aplastic Anemia	
Secondary	Fanconi's anemia
Radiation	Dyskeratosis congenita
Drugs and chemicals	Shwachman-Diamond syndrome
Regular effects	Reticular dysgenesis
Idiosyncratic reactions	Amegakaryocytic thrombocytopenia
Viruses	Familial aplastic anemias
Epstein-Barr virus (infectious mononucleosis)	Preleukemia (monosomy 7, etc.)
Hepatitis (non-A, non-B, non-C hepatitis)	Nonhematologic syndrome (Down's, Dubowitz, Seckel)
Parvovirus B19 (transient aplastic crisis, PRCA)	
HIV-1 (AIDS)	
Immune diseases	
Eosinophilic fasciitis	
Hypoimmunoglobulinemia	
Thymoma/thymic carcinoma	
Graft-versus-host disease in immunodeficiency	
Paroxysmal nocturnal hemoglobinuria	
Pregnancy	
Idiopathic	

42.Ans.C

Table 102-1 Differential Diagnosis of Pancytopenia
Pancytopenia with Hypocellular Bone Marrow
Acquired aplastic anemia

Constitutional aplastic anemia (Fanconi's anemia, dyskeratosis congenita) Some myelodysplasia Rare aleukemic leukemia (AML) Some acute lymphoid leukemia Some lymphomas of bone marrow	
Pancytopenia with Cellular Bone Marrow	
Primary bone marrow diseases Myelodysplasia Paroxysmal nocturnal hemoglobinuria Myelofibrosis Some aleukemic leukemia Myelophthisis Bone marrow lymphoma Hairy cell leukemia	Secondary to systemic diseases Systemic lupus erythematosus Hypersplenism B_{12}, folate deficiency Overwhelming infection Alcohol Brucellosis Sarcoidosis Tuberculosis Leishmaniasis
Hypocellular Bone Marrow ± Cytopenia	
Q fever Legionnaires' disease Anorexia nervosa, starvation *Mycobacteria*	

43.Ans.C

44.Ans.D
It is the treatment of choice in young patient with fully histocompatible sibling donor
Survival among children 80%
Morbidity and mortality of Transplants increase with age
Immunosuppression is TOC in patient who lack suitable donor done with ATG + Cyclosporin

45.Ans.B
Hepatitis responsible for 5% of all cases
Hepatitis seronegative (Non A, non B, non C & non G)
Presumably due to a novel yet undiscovered virus
Parvo virus B19 causes Transient aplastic crises hemolytic anemias but deos't cause generalized bone marrow failure
Presence of giant pro normoblast is cytopathic sign of parvo infection

46.Ans.A
Weight loss points to other etiologies of pancytopenia

47.Ans D
The myelodysplasias (MDSs) are a heterogeneous group of hematologic disorders broadly characterized by cytopenias associated with a dysmorphic (or abnormal appearing) and usually cellular bone marrow, and by consequent ineffective blood cell production.
A clinically useful nosology of these entities was first developed by the French-American-British Cooperative Group in 1983.
Five entities were defined: refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-t), and chronic myelomonocytic leukemia (CMML).
Idiopathic MDS is a disease of the elderly; the mean age at onset is 68 years.
There is a slight male preponderance

Cytogenetic abnormalities are not random (loss of all or part of 5, 7, and 20, trisomy of 8) and may be related to etiology (11q23 following topoisomerase II inhibitors); chronic myelomonocytic leukemia is often associated with t(5;12)
The median survival varies greatly from years for patients with 5q– or sideroblastic anemia to a few months in refractory anemia with excess blasts or severe pancytopenia associated with monosomy 7
Anemia is present in the majority of cases, either alone or as part of bi- or pancytopenia; isolated neutropenia or thrombocytopenia is more unusual.
Macrocytosis is common, and the smear may be dimorphic with a distinctive population of large red blood cells. Platelets are also large and lack granules
The bone marrow is usually normal or hypercellular, but in 20% of cases it is sufficiently hypocellular to be confused with aplasia
The World Health Organization considers the presence of 20% blasts in the marrow as the criterion that separates acute myeloid leukemia from MDS.
The therapy of MDS has been unsatisfactory. Only stem cell transplantation offers cure: survival rates of 50% at 3 years have been reported.
Azacitidine improves blood counts and modestly improves survival in about 16% of MDS patients
Azacitidine is directly cytotoxic but also inhibits DNA methylation, thereby altering gene expression.
Thalidomide, lenalidomide, amifostine also used in treatment

48. Ans.B

Table 58-2 Red Blood Cell Indices	
Index	**Normal Value**
Mean cell volume (MCV) = (hematocrit x 10)/(red cell count x 10^6)	90 ± 8 fL
Mean cell hemoglobin (MCH) = (hemoglobin x 10)/(red cell count x 10^6)	30 ± 3 pg
Mean cell hemoglobin concentration = (hemoglobin x 10)/hematocrit, or MCH/MCV	33 ± 2%

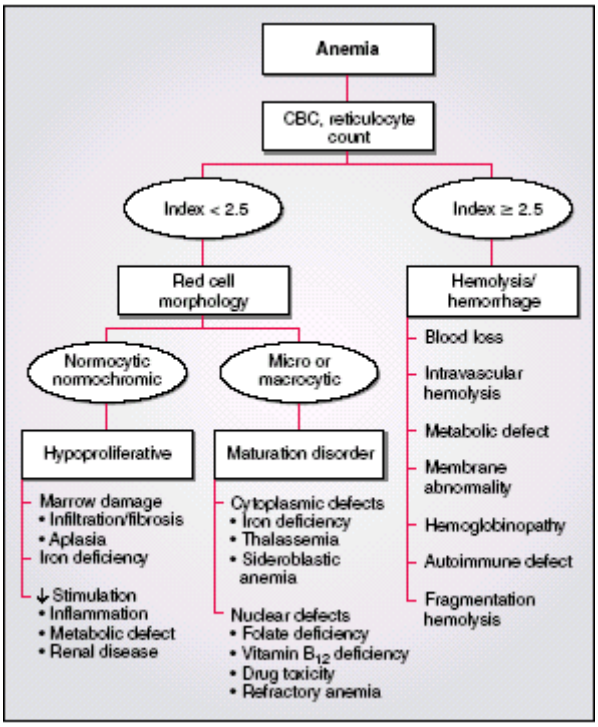
49. Ans.B

Table 58-4 Calculation of Reticulocyte Production Index
Correction #1 for anemia: This correction produces the corrected reticulocyte count In a person whose reticulocyte count is 9%, hemoglobin 7.5 g/dL, hematocrit 23%, the absolute reticulocyte count = 9 x (7.5/15) [or x (23/45)]= 4.5% Correction #2 for longer life of prematurely released reticulocytes in the blood: This correction produces the reticulocyte production index In a person whose reticulocyte count is 9%, hemoglobin 7.5 gm/dL, hematocrit 23%, the reticulocyte production index

First correction adjust Reticulocyte count based on decreased number of circulating red cells
Second correction for longer life of prematurely released Reticulocyte

50. And.B

MED 5



Maturation disorders are identified form discrepancy between M/E ratio and Reticulocyte production index