ANEMIA:

Anemia is the condition in which the oxygen carrying capacity of blood is reduced. In the anemia the total number of RBCs decreases so indirectly decreases the oxygen level so decrease the production of ATP and energy.

GENERAL PATHOPHYSIOLOGY OF ANEMIA:

Our blood contains RBCs

↓

RBCs contains Hb

↓

Hb contains the iron

↓

Iron transfer the oxygen in body

↓

Oxygen is useful for production of ATP and Heat

↓

ATP provide energy

Anemia is not a single disease entity but a sign of disease. Independent of the cause, anemia is associated with a reduction in circulating Hb because of reduced number of erythrocytes or less Hb per erythrocytes. The number of erythrocytes varies with age, sex and atmospheric pressure.

CAUSES:

The main causes of anemia are:

1. Blood loss 2. Lack of red blood cell production 3. High rates of red blood cell destruction

The other causes for the anemia are as under:

Blood Loss

- Blood loss is the most common cause of anemia, especially iron-deficiency anemia. Blood loss can be short term or persist over time.
- Heavy menstrual periods or bleeding in the digestive or urinary tract can cause blood loss. Surgery, trauma, or cancer also can cause blood loss.
- If a lot of blood is lost, the body may lose enough red blood cells to cause anemia.

Lack of Red Blood Cell Production

- Both acquired and inherited conditions and factors can prevent your body from making enough red blood cells. "Acquired" means you aren't born with the condition, but you develop it. "Inherited" means your parents passed the gene for the condition on to you.
- Acquired conditions and factors that can lead to anemia include poor diet, abnormal hormone levels, some chronic (ongoing) diseases, and pregnancy.
- Aplastic anemia also can prevent your body from making enough red blood cells. This condition can be acquired or inherited.

Diet

- A diet that lacks iron, folic acid (folate), or vitamin B12 can prevent your body from making enough red blood cells. Your body also needs small amounts of vitamin C, riboflavin, and copper to make red blood cells.
- Conditions that make it hard for your body to absorb nutrients also can prevent your body from making enough red blood cells.

Hormones

- Our body needs the hormone erythropoietin (eh-rith-ro-POY-eh-tin) to make red blood cells. This hormone stimulates the bone marrow to make these cells. A low level of this hormone can lead to anemia.

Diseases and disease treatments

- Chronic diseases, like kidney disease and cancer, can make it hard for your body to make enough red blood cells.
- Some cancer treatments may damage the bone marrow or damage the red blood cells' ability to carry oxygen. If the bone marrow is damaged, it can't make red blood cells fast enough to replace the ones that die or are destroyed.
- People who have HIV/AIDS may develop anemia due to infections or medicines used to treat their diseases.

Pregnancy

- Anemia can occur during pregnancy due to low levels of iron and folic acid and changes in the blood.
- During the first 6 months of pregnancy, the fluid portion of a woman's blood (the plasma) increases faster than the number of red blood cells. This dilutes the blood and can lead to anemia.

Aplastic anemia

- Some infants are born without the ability to make enough red blood cells. This condition is called aplastic anemia. Infants and children who have aplastic anemia often need blood transfusions to increase the number of red blood cells in their blood.
- Acquired conditions or factors, such as certain medicines, toxins, and infectious diseases, also can cause aplastic anemia.

High rates of red blood cell destruction

- Both acquired and inherited conditions and factors can cause your body to destroy too many red blood cells. One example of an acquired condition is an enlarged or diseased spleen.
- The spleen is an organ that removes worn out red blood cells from the body. If the spleen is enlarged or diseased, it may remove more red blood cells than normal, causing anemia.
- Examples of inherited conditions that can cause your body to destroy too many red blood cells include sickle cell anemia, thalassemias, and lack of certain enzymes. These conditions create defects in the red blood cells that cause them to die faster than healthy red blood cells.
- Hemolytic anemia is another example of a condition in which your body destroys too many red blood cells. Inherited or acquired conditions or factors can cause hemolytic anemia. Examples include immune disorders, infections, certain medicines, or reactions to blood transfusions.

SIGNS & SYMPTOMS:

Common symptoms of anemia:

- fatigue
- decreased energy
- weakness
- shortness of breath
- light headedness
- palpitations (feeling of the heart racing or beating irregularly) and
- looking pale

Symptoms of severe anemia may include:

- chest pain, angina, or heart attack
- dizziness
- fainting or passing out; and
- rapid heart rate.

Some of the signs that may indicate anemia in an individual may include:

- Change in stool color, including black and tarry stools (sticky and foul smelling), maroon-colored, or visibly bloody stools if the anemia is due to blood loss through the gastrointestinal tract;
- rapid heart rate;
- low blood pressure;
- rapid breathing;
- pale or cold skin;
- yellow skin called jaundice if anemia is due to red blood cell breakdown;
- heart murmur; and
- enlargement of the spleen with certain causes of anemia.

NORMAL HEMOGLOBINE VALUE AS PER AGE AND SEX:

Age & Sex	Mean Hb (g/dl)
1-3 days	16.0 – 19.0
6 Months – 2 Yrs	12.0 – 14.5
12 – 18 Yrs Male Female	 14.5 – 17.0 12.5 – 14.0
Adult Male Female	 15.5 – 17.0 13.0 – 15.0

Note: Atmospheric pressure:

- People at high altitudes have more erythrocytes than at low altitudes.

NORMAL HEMATOLOGIC & BIOCHEMICAL PARAMETERS:

Component	**Conventional**
Hematologic	
Hematocrit (Ratio of RBC-Blood Vol.) Male Female	 45 – 52 % 37 – 48 %
Hemoglobin Male Female	 14 – 18 g /dL 12 – 15 g/dL
Erythrocyte count	4.2 -5.9 x 10^6/mm
Reticulocyte count	0.5 – 1.5 %
MCV	80 – 90 fmol
MCH	27 – 30 pg
MCHC	32 – 36 g/dL
RDW	11.5 – 14.5 %

Biochemical	
Iron Male Female	 80 – 200 mcg/dL 60 – 190 mcg/dL
Transferrin	170 – 370 mg/dL
TIBC	250 – 410 g/ml
Transferrin saturation	20 – 55 %
Transferrin receptors	2.8 – 8.5 mg/L
Ferritin	1.5 – 30 mcg/dL
Zinc protoporphyrin	<70 mcg/dL red cell
Folate Normal Borderline	 2 – 10 ng/ml 1 - 1.9 ng/ml
Vitamin B12	200 – 1000pg/ml
Methylmalonic acid	53 – 376 nmol/ L
Homocysteine	4.1 – 21.3 mcmol / L

DIAGNOSIS:

A detailed medical & medication history along with hematologic & biochemical tests is obtained.

I. Hematologic tests:

It includes blood Hb concentration, cell counts, mean corpuscular volume (MCV), Hct, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), etc.

1. **MCV → cell size**

   Microcytic anemia - < 80fL

   Macrocytic anemia - >100fL

2. **MCH & MCHC → cell colour**

   Hypochromic anemia - low MCHC

   Hyperchromic anemia - high MCHC

3. **Red blood cell distribution width (RDW) → variation in erythrocyte size in blood sample**

   Iron deficiency anemia → increased RDW

4. **Reticulocyte counts → bone marrow activity**

   Iron, B12 or folic acid therapy for respective deficiency states → reticulocytosis

5. **Others :** differential white cell count, platelet count, microscopic examination of peripheral blood smears & bone marrow aspirates.

II. Biochemical tests:

It includes measurement of serum vitamin conc, transport proteins, saturation of protein binding sites & storage amounts.

TYPES OF ANEMIA

CLASSIFIED ACCORDING TO THE SIZE OF THE RED BLOOD CELLS:

a) **Microcytic anemia**:

- If the red blood cells are smaller than normal, this is called **microcytic anemia**. The major causes of this type are iron deficiency (low level iron) anemia and thalassemia (inherited disorders of hemoglobin).

b) Normocytic anemia

- If the red blood cells size are normal in size (but low in number), this is called **normocytic anemia**, such as anemia that accompanies chronic disease or anemia related to kidney disease.

c) Macrocytic anemia

- If red blood cells are larger than normal, then it is called **macrocytic anemia**. Major causes of this type are pernicious anemia and anemia related to alcoholism.

ACCORDING TO THE CAUSE, ANEMIA ARE CLASSIFIED AS UNDER:

A) IRON DEFICIENCY ANEMIA:

- It is cause by excessive loss of iron or inadequate absorption of iron.
- It is most often in female than male.
- Iron absorption is regulated by iron needs & body stores.
- When iron stores are low, higher proportion of available iron is absorbed & vice versa. Except, in primary hemochromatosis, thalassemia & sideroblastic anemia iron absorption remains normal & even elevated despite increased iron stores.
- It is primarily absorbed in upper duodenum.

PATHOPHYSIOLOGY OF IRON DEFICIENCY ANEMIA:

- Iron is an essential element for erythropoiesis, tissue respiration & several enzyme catalyzed reactions. The average adult body contains 3 to 5 g elemental iron.
- Iron is distributed in body in two forms: functional & storage.

I . Functional iron

It exists as Hb , little as myoglobin , transferring & tissue enzymes.

- Hb is the oxygen binding protein that transports oxygen from lungs to tissues.
- Myoglobin, a hemo protein in muscle accepts oxygen from hemoglobin in the peripheries & acts as an oxygen store in muscle. If oxygen supply is limited, it releases oxygen to cytochrome oxidase leading to oxidative phosphorylation.
- Transferrin is a specific iron binding protein that transports iron through plasma & extravascular spaces. Each molecule of transferrin binds 2 molecules of iron in ferric state. The TIBC is high in iron deficiency & low in iron overload.

II. Storage iron:

- It is in the form of ferritin & hemosiderin, which is located in parenchymal cells of liver & reticuloendothelial cells of the bone marrow, spleen & liver.
- Low iron stores are an early sign of iron deficiency & may help differentiate between iron deficiency anemia & other causes of anemia.

DAILY IRON NEEDS:

Recommended daily allowances of iron:

category	**Age (Yr)**	**Iron (mg)**
Infants	0 – 0.5	6
	0.5 - 1	10
Children	1 - 10	10
Boys & men	11 - 18	12
	> 19	10
Girls & women	11 - 50	15
	> 51	10
Pregnant women		30
Lactating women		15

FACTORS ASSOCIATED WITH IRON ABSORPTION:

Factor	**Associations**
Promoting absorption	
Inorganic iron	Ferrous form is better absorbed than ferric iron & organically bound iron.
Ascorbic acid	Convert ferric iron to ferrous iron
Acids	Gastric HCl promotes the release & conversion of dietary iron to the ferrous form
Chelates	Iron chelated to low mol wt sub (sugars, amino acids, succinates) facilitates iron binding to the intestinal mucosa
Clinical states	Iron deficiency, increased erythropoiesis, pregnancy, anoxia & pyridoxine deficiency
Reducing absorption	
Alkaline	Antacids, alkaline pancreatic secretions containing phosphate convert iron to insoluble ferric hydroxide
Dietary	Dietary phosphates & phytates in cereals & tannins in tea probably complex iron
Clinical states	Chronic diarrhea, steatorrhea, adequate iron stores,decreased erythropoiesis, acute or chronic inflammation

FACTORS ASSOCIATED WITH IRON DEFICIENCY:

Factor	**Association**
Dietary	Starvation, poverty, vegetarianism, religious practice, food pads
Blood loss : Women & Girls General	 Menstruation, postmenopausal bleeding, pregnancy Esophageal varices, peptic ulcer, drug induced gastritis, carcinomas of colon & stomach, ulcerative colitis, hemorrhoids, renal or bladder lesions, hookworm infestations, frequent blood donation, athletic training, widespread bleeding disorders
Malabsorption	Celiac disease, partial & total gastrectomy, chronic inflammation
Increased requirements	Rapid growth, pregnancy

SIGNS & SYMPTOMS:

- Developmental delays
- Behavioral disturbances
- Altered central nervous system development
- Impaired work capacity
- Preterm delivery
- Delivery of low birth weight baby

- Others like brittle or spoon shaped nails, angular stomatitis, atrophic tongue & pharyngeal & esophageal webs causing dysphagia & atrophic gastric mucosa.

DIAGNOSIS:

- Medical history, full blood count & peripheral smears.
- Blood Hb concentrations & erythrocyte numbers are normal in mild cases.
- As deficiency worsens MCV & erythrocyte count & Hb decreases & RDW increases.
- Hypochromia or poikilocytosis shown when Hb conc are 7.0 g/dl or less for women & g/dl or less for men.
- Absence of stainable iron in bone marrow aspirates is ultimate proof of deficiency but is painful & expensive so not used routinely.
- After hemorrhage or iron therapy reticulocytes increase.
- Serum ferritin is the first parameter to change in iron deficiency. It fall (< 15 mcg/ml) in deficiency but increase abnormally in iron storage conditions.
- ZPP (zinc protoporphyrin)→ is an early indicator of iron deficient erythropoiesis than anemia. It represents the amount of protoporphyrin not incorporated into heme, it increase when insufficient iron is available for Hb synthesis.
- TfR (transferring receptor)→ provides information on later stages of iron deficiency, increasing only after iron stores are depleted.
- Since ZPP & TfR are not affected by inflammatory processes are useful in differentiating it from iron deficiency anemia.
- Serum iron is low & TIBC is high.

PREVENTION:

It can be done by identifying the underlying cause of iron deficiency & correcting it through diet or supplementation.

- **Dietary manipulation :**

- Food fortification is best recommended.
- When dietary iron supplementation is not possible or adequate, oral supplementation should be initiated.
- In **infants** CDC recommends following guidelines :
    1. breastfeeding for 4 – 6 months after birth.

2. use of 1 mg/kg/day of iron from supplemental foods or iron drops when breastfeeding is stopped.
3. use of only iron fortified infant formula as a substitute for breast milk.
4. use of 2 – 4 mg/kg/day of iron drops (max 15mg/day) for preterm or low birth weight infants starting at 1 mth & continuing until 12 mths after birth.
5. introduction of iron fortified infant cereal at age 4 to 6 mths.

- The CDC recommends universal treatment with 30 mg iron/day during **pregnancy** to prevent iron deficiency.but since iron can cause side effects & potentially affect absorption of other nutrients, it is recommended only for women at risk of iron deficiency anemia.

Screening of iron deficiency:

- The CDC recommends screening of infants who are at risk (preterm, low birth weight, low iron diet) at 9 to 12 mths & at 15 to 18 mths of age.
- Women with risk factors (poor diet, excessive menstrual bleeding, chronic blood loss) should be screened annually.

TREATMENT:

1. **Oral iron therapy** :

- Generally, 30 to 40 mg elemental iron is used to treat iron deficiency states.
- This can be calculated from maximum rate of Hb regeneration. 0.25 g Hb/100 ml blood/ day x 5000 ml blood x 3.4 mg Fe/1g Hb = 40 mg Fe/day
- Since only 10 to 20 % of iron is absorbed, 200 to 400 mg iron would result in absorption of 40 mg elemental iron.
- Maximum absorption occurs if iron is taken before meals or between meals.

Side effects:

- It includes epigastric distress, abdominal cramping, nausea, diarrhoea & constipation caused by gastric irritation.
- This can be minimized by reducing daily dosage, taking the iron with food or changing to once a week dosing.
- Use of enteric coated products to minimize the side effects is not preferred since it prevents the dissolution & so decrease the absorption.

- Iron therapy can also cause the stools to appear black about which patients should be educated to differentiate from that of GI bleeding.

Drawbacks:

- Iron absorption may be reduced in patients with reduced gastric acid production or prior GI surgeries.
- When an ability to absorb iron is suspected, oral bolus dose of 325 mg ferrous sulphate should be administered. The serum iron levels after 2 & 4 hours should be 21 to 23 mcmol/ L. otherwise it indicates decreased iron absorption.
- Antacids, H 2 blockers & proton pump inhibitors may also decrease iron absorption
- Fails in cases of malabsorption, non-compliance with oral iron therapy, severe uncontrolled intolerance to iron therapy, excessive iron loss or erythropoiesis as seen in patients on renal dialysis receiving erythropoietin.

***common oral iron preparations includes salts of iron such as ferrous sulphate, ferrous fumarate, ferrous gluconate, etc

2. parenteral iron therapy :

To overcome the drawbacks of iron therapy, parenteral iron therapy is preferred.

- The amount of parenteral iron needed to replenish iron stores & restore Hb levels in patients with iron deficiency anemia can be obtained by formula :
  - Dosage (mg) = 0.3 x body weight (lb) x [100- {Hb (g/dl) x 100/14.8}]
    Or
  - Dosage (mg) = 0.66 x body weight (kg) x [100-(Hb{g/dl} x 100/14.8}]
- The iron dose calculated is divided by 50 mg iron / ml to provide the volume of iron dextran injection needed.
- For children weighing < 15 kg, a normal mean of Hb of 12g/L is used in place of 14.8 g/dL.
- To determine iron replacement dosage in patients with active blood loss, one assumes that 1 ml of normochromic, normocytic erythrocytes contains 1 mg elemental iron :
  - Dosage (mg) = 1 mg iron / ml blood x blood loss (ml) x Hct
- It is administered by deep IM inj into the upper quadrant of the buttock or IV, eitheras a bolus or a total dose infusion (TDI).

Contraindications to iron therapy:

- In hemochromatosis & hemosiderosis (iron load)
- In thalassemia & anemic conditions with chronic inflammatory disease such as rheumatoid arthritis (have normal to high iron stores due to impaired use of iron)
- In alcoholics (elevated iron stores)
- In enteritis, diverticulitis, colitis & ulcerative colitis (local effects)
- In patients receiving repeated blood transfusions.

Iron toxicity:

- It can be acute (overdose or accidental poisoning) or chronic (hemochromatosis, hemosiderosis, thalassemia)
- An iron overloaded person usually have more than 4 g body iron.
- Computed tomography & magnetic resonance imaging have been used to determine hepatic iron content.

  Causes

  - Alcohol consumption
  - Fortified food may be good for women but may lead to excessive iron intake by men.
  - Iron overload secondary to anemia :
    1. hypoplastic bone marrow → blood transfusion (eg. Aplastic anemia)
    2. hyperplastic bone marrow → increased iron absorption secondary to ineffective erythropoiesis (eg. Thalassemia major, sideroblastic anemia, some hemolytic anemia)
- Treatment of tranfusional iron overload generally consist of chelation therapy such as deferoxamine.

B) MEGALOBLASTIC ANEMIA/PERNICIOUS ANEMIA:

- It is cause by insufficient of hemopoiesis.
- In this condition stomach decreases the production of intrinsic factors because they decrease the absorption of vitamin B_{12}.
- It is a sub class of the macrocytic anemias.
- It is characterized by a lowered blood Hb mass due to reduced erythropoiesis secondary to defective DNA synthesis in the developing erythroid cells of the bone marrow.

CAUSES:

- It can be mainly due to deficiencies of **vitamin B12 and folate.**
- It can be by drug induced interferences, either direct or indirect, i.e. with DNA synthesis or nutritional status.

1. VITAMIN B12 DEFICIENCY MEGALOBLASTIC ANEMIA:

Stages of vitamin B12 deficiency anemia:

Stage	B12 concentration	MCV	Hb	Signs & symptoms
Normal	Normal	Normal	Normal	None
Negative balance	Normal	Normal	Normal	None
Depletion of stores	Slight decrease	Normal	Normal	Possible
B12 deficient erythropoiesis	Mod decrease	Increased	Normal	Possible
B12 deficiency anemia	Severe decrease	Increased	Decreased	Probable

Vitamin B12 Needs:

1. Daily requirement for humans is 0.5 to 1 mcg.
2. The total body stores amount to 2-5 mg mainly into liver.

PATHOGENESIS OF MEGALOBLASTIC ANAEMIA DUE TO VIT B12:

- Vit B 12 is well absorbed from GIT in a sequence by three different binding proteins i.e. R proteins, IF, & transcobalamin II (TCII).
- Extravascular R proteins also known as cobalophilins, are the first binding proteins for B12.

- The cobalamin remains bound to R protein in the upper small intestine until pancreatic proteases viz, trypsin partially degrade the complex releasing B12.
- Then B12 binds to IF, a specific B12 binding glycoprotein.
- The IF – B12 complex is highly resistant to proteolysis, passes down the small intestine to the distal ileum where it attaches to specific receptors.
- This attachment with receptor is not energy dependent but requires extracellular calcium & pH higher than 5.4.
- The majority of B12 in the circulation binds to intravascular R protein i.e. transcobalamin I (haptocorrin).
- But transcobalamin II (TCII) is a functional binding protein responsible for releasing B12 to the tissues.
- Patients with TC II deficiency may have normal serum B12 concentration as binding to TC I compensates for it.
- Features of severe B12 deficiency occur as TCI – B12 complex does not deliver the vitamin to the tissues.
- Another mechanism of absorption is diffusion, which is a potential method of providing oral B12 therapy to people with low IF levels (pernicious anemia).
- Lack of B12 allows folic acid to be trapped as non-functional methyl tetrahydrofolate(folate trap) So deficiency of functional FH4 causes impairment of formation of deoxy thymidine monophosphate(dTMP) which is needed for DNA synthesis As a result large proerythroblast fails to divide rapidly to make mature RBC rather immature precursors of erythocyte(blast cell) appear to cause megaloblastic anaemia.

ETIOLOGY:

I Dietary → inadequate intake.

II Impaired transport → transcobalamin II deficiency

III Malabsorption:

- **Pernicious anemia**: It is a B12 malabsorption caused by the loss of gastric IF secretion. Its an auto immune reaction against gastric parietal cells.
- **Gastric disorders:** gastrectomy (absolute deficiency of IF), atrophic gastritis, achlorhydria, vagotomy, partial gastrectomy & the use of H 2 receptor antagonists (prevent release of vitamin from food).

- **Intestinal problems**: Zollinger – Ellison syndrome, surgical resection or bypass of the ileum, Crohn's disease, celiac disease, lymphomas, Whipple's disease, bacterial overgrowth.
- **Drug induced**: colchicine, PAS, neomycin, H2 blockers, proton pump inhibitors, ethanol, Cholestyramine, etc decrease vitamin B12 absorption.

SIGNS & SYMPTOMS:

- Peripheral neuropathy
- Strange feeling in extremities
- Loss of hand coordination
- Deterioration in hand writing
- Tingling of extremities
- Loss of propioception
- Depression
- Psychosis
- Spinal cord degeneration
- Sore tongue or mouth, glossitis, beefy red tongue
- Lateral column disruption results in weakness & spasticity, exemplified by myoclonus, hyperreflexia, & a positive Babanski's sign. If it remains untreated, instability of gait & virtual paralysis results.

DIAGNOSIS:

- Measurement of holo - TC to differentiate between B12 deficiency or TC II deficiency. But clinically not used because of limited assay availability.
- **TC II saturation**→ it decreases in early B12 deficiency.
- Assessment of metabolite production – **MMA & Hcy** where MMA is more specific for B12 deficiency. But MMA also increases in renal disease so renal function should be assessed.
- **MCV** > 100 fL indicating macrocytosis indicates its deficiency.
- **Schilling test** (with or without IF)

- Stage I → An oral dose of Co labeled B12 is given, followed by an IM dose of unlabelled B12. The large IM dose saturates B12 binding proteins in the blood. So there are few finding sites for labeled B12 & a substantial portion is excreted in urine.

Urine is collected over 24 hours & the amt of labeled B12 is measured. If B12 conc is less than 10 % absorption is impaired & if its <5% than it indicates pernicious anemia.

- Stage II → Same process is repeated but now IF is given with labeled B12.If IF deficiency is there than stage I will be abnormal & stage II will be normal.
- Stage III → Patients are given antibiotics (tetracycline). So if there is bacterial overload stage I & II will be abnormal & stage III will be normal.
- If all the stages show abnormal absorption, it indicates ileal disorder.
- Results of test :

Condition	Stage I	Stage II	Stage III
Normal	Normal		
Inadequate diet	Normal		
Pernicious anemia	Low	Normal	
Bacterial overgrowth	Low	Low	Normal
Ileal defect	Low	Low	Low

- **Evaluating smear for megaloblastic changes** viz, neutrophil hypersegmentation & oval shaped erythrocytes, generally differentiates a B12 or folate deficiency from other causes.
- If iron deficiency occurs with vit B12, the MCV may appear normal but the blood smear should show both megaloblastic & microcytic cells.
- **Others** : thymidine uptake (deoxyuridine suppression test [DUST]) by bone marrow cells, food cobalamin absorption, erythropoietin measurement, folate concentrations & gastrin & pepsinogen analysis.

TREATMENT:

- Identify B12 deficiency early (before anemia or neurologic symptoms develop)
- Correct the cause of deficiency if possible
- Replenish the depleted stores
- If necessary administer maintenance B12 therapy
- Dietary changes & supplemental B12 given orally, intranasally or parenterally.

PHARMACOTHERAPY:

1. **Oral vitamin B12 therapy :**

- Usual oral dose of vitamin B12 supplementation is 1 to 10 mcg/day.
- In patients with malabsorption, B12 dosages should be 1000 mcg or higher to produce favorable long term results.
- Concerns with oral therapy are the potential for erratic absorption, poor compliance & subsequent development of neurologic symptoms.
- Patient evaluation & monitoring for compliance & therapeutic response should whether long term oral therapy is optimal for each patient.
- Preparations containing iron in different forms are used eg. Ferrous fumarate, ferrous gluconate, etc.

2. **Parenteral vitamin B12 therapy :**

- Being safe, dosages of 100 to 1000 mcg can be given.
- It is given **IM** or by deep **Sc** injection .
- Peak serum concentrations after IM are reached in about 1 hr.
- The half-life of the parenteral B12 is about 6 days & its half-life in liver is 400 days.
- Two synthetic forms of B12 are available: **cyanocobalamin & hydroxocobalamin.**
- Hydroxocobalamin is more protein bound & so requires less frequent dosing. Cyanocobalamin has a side effect of optic neuropathy.
- It is well tolerated & has fewer allergic & anaphylactic reactions.
- Iron dextran is commonly used.

3. **Intranasal Vitamin B12 therapy:**

- Intranasal sprays & gels are available for patients who refuse or cannot tolerate parenteral therapy & don't respond to oral treatment.

2. FOLATE DEFICIENCY MEGALOBLASTIC ANEMIA:

- Folate deficiency occurs in stages, with depletion of stores leading to deficiency that can result in megaloblastic anemia & other hematologic abnormalities.
- Role of folate deficiency is evaluated in pregnancy, heart disease, stroke & peripheral arterial disease.

PATHOPHYSIOLOGY OF FOLATE RELATED MEGALOBLASTIC ANEMIA:

- Dietary folate is usually in polyglutamate form, which must be converted to monoglutamate form for absorption.
- Active absorption of dietary folate occurs mainly in the proximal part of the small intestine.
- Synthetic folate is already in monoglutamate form & has greater stability & better absorption.
- Folic acid from formulations is completely absorbed in the upper duodenum, even in the presence of malabsorption.
- The principle circulating form is extensively protein bound & undergoes enterohepatic cycling but not reabsorbed from the bile.
- Reduced form of folate (tetrahydrofolate) are cofactors for transformylation reactions in the biosynthesis of purines & thymidylates of nucleic acids.
- Folate deficiency, so leads to defective DNA synthesis resulting in megaloblast formation & bone marrow suppression.
- It is needed in Hcy metabolism or any other methylation reactions.

FOLATE NEEDS:

- The minimum daily requirement of folate is 50 to 100 mcg/day in general & in pregnancy an additional 400 mcg/ day is recommended.
- The average amount stored in the body is 5 to 10 mg, one half of which is found in liver.

EPIDEMIOLOGY:

- Malnutrition
- In alcoholics due to poor diet & altered absorption.
- In pregnancy folate needs increase thrice the normal requirement due to large increase in nucleic acid synthesis associated with growth of the fetus, placenta & uterus & with increased maternal erythrocyte mass.
- Folate needs also increase during malignancy, increased erythropoiesis, conditions causing rapid cell turnover, chronic hemolytic anemia, exfoliative dermatitis, generalized psoriasis or extensive burns.

- Drugs can also cause folate deficiency by either reducing absorption or by altering metabolism.
  - Reduced absorption → ethanol, metformin, oral contraceptives, Sulfasalazine, sulfamethoxazole
- Altered metabolism → methotrexate, trimethoprim, triamterene, alcohol

SIGNS & SYMPTOMS:

- They are similar to those of other anemias.
- In addition may cause megaloblastosis, glossitis, diarrhoea & weight loss.

DIAGNOSIS:

- Serum or erythrocyte **folate concentrations** are assessed where erythrocyte folate concentration reflects tissue status & is a better indicator of depletion.
- **Hcy concentration** is increased in deficiency. (also increased in B12 deficiency & decreased renal function)
- A blood smear & hematologic evaluation show macrocytosis with megaloblastosis.(also shown by B12 deficiency).

TREATMENT:

- Primary prevention is by dietary manipulation or oral supplementation.
- Women planning to become pregnant should take atleast 400 mcg/ day, to prevent fetal neural tube defects.
- Folate deficiency is usually treated with oral folic acid 1 mg daily.
- Parenteral administration is indicated when oral administration is unacceptable or not possible.
- Long term therapy is needed in chronic hemolytic states, myelofibrosis, refractory malabsorption, postgastrectomy states, prolonged stress or infection, chronic fever & persistent diarrhoea.

C. ANEMIA OF RENAL FAILURE:

- The severity of the anemia correlates with the extent of uremia.
- Most of the patients with serum creatinine concentration higher than 310mcmol/L & 97% of those on maintenance dialysis are affected.
- The cells are normochromic & normocytic but often are irregular in shape.

PATHOPHYSIOLOGY:

- It is a multifactorial process but primarily due to reduced secretion of erythropoietin by the diseased kidneys.
- **Accumulation of the inhibitors of erythropoiesis, reduced RBC life span & chronic blood loss.**
- Parathyroid hormone & the polyamine spermine have been implicated in reducing marrow responsiveness to erythropoietin.
- Erythrocyte survival also decreases to an average of one-half of normal uremia due to mild, chronic hemolysis.
- Chronic blood loss both from a GI source & during hemodialysis may also contribute to it.
- Others: folic acid deficiency caused by losses to the dialysate, the accumulation of fat sol vit A, aluminum toxicity caused by long term hemodialysis & the use of aluminum containing phosphate binders & osteitis fibrosa, a complication of hyperparathyroidism in which myelofibrosis reduces viable erythroid cellular mass.

TREATMENT:

- Iron & folate supplementation should be provided as necessary, & blood loss & use of aluminum containing antacids should be minimized whenever possible.
- For treatment of acute symptoms of hypoxia transfusions of RBCs is done.
- Risks of transfusions : Hs reactions, transmission of viral hepatitis, bone marrow suppression, iron overload, etc.
- Drugs : androgens, recombinant human erythropoietin, etc.

D. APLASTIC ANEMIA

- Aplastic anemia is distinguished by hypocellularity of the bone marrow & subsequent pancytopenia that is unrelated to malignancy or myeloproliferative disease.
- The characteristic anemia , neutropenia & thrombocytopenia result from failure of the pluripotent stem cells due to congenital or acquired process.

ETIOLOGY:

- It is mostly idiopathic.
- Myelosuppression is a component of several congenital disease but is more commonly acquired after exposure to :

- drugs (chloramphenicol, anticonvulsants, acetazolamide, etc)
- chemicals (arsenic, benzene, ethanol, etc)
- viral (HIV, influenza, rubella etc)
- others (ionizing radiation, pregnancy, mycobacterial infection, etc.)

PATHOPHYSIOLOGY :

- It develops when hematopoiesis is interrupted because of deficient or defective stem cells.
- Others : immune mediated suppression of stem cell function, disturbances in the bone marrow microenvironment, & alterations in the cellular or humoral interactions that normally sustain hematopoiesis.

CLINICAL PRESENTATION:

- Pallor & fatigue initially mild but more pronounced when accompanied by bleeding due to thrombocytopenia.
- Ecchymoses & petechiae
- Fever due to infection caused by underlying neutropenia.

DIAGNOSIS:

- Peripheral blood - ↓ number of morphologically normal cells.
- Erythrocytes – normochromic, normocytic or slightly macrocytic
- Reticulocyte count, absolute granulocyte count - ↓
- Bone marrow biopsy – extensive areas of hypocellularity interspersed with small patches of hematopoietic cells.

TREATMENT:

- Removal of potential causative agents, supportive care & restoration with normal hematopoiesis with pharmacologic therapy or BMT.
- Blood transfusions, preferably with leukocyte depleted products, antiplatelet antibodies, broad spectrum antibiotics, cyclophosphamide, androgens, hematopoietic growth factors.

PRECAUTIONS FOR TREATMENT:

- Blood products from family members should not be used in candidates for marrow transplantation.
- Due to risk of hematoma, IM inj should be avoided in patients with thrombocytopenia & so should be avoided aspirin, NSAIDS & other agents with antiplatelet properties.

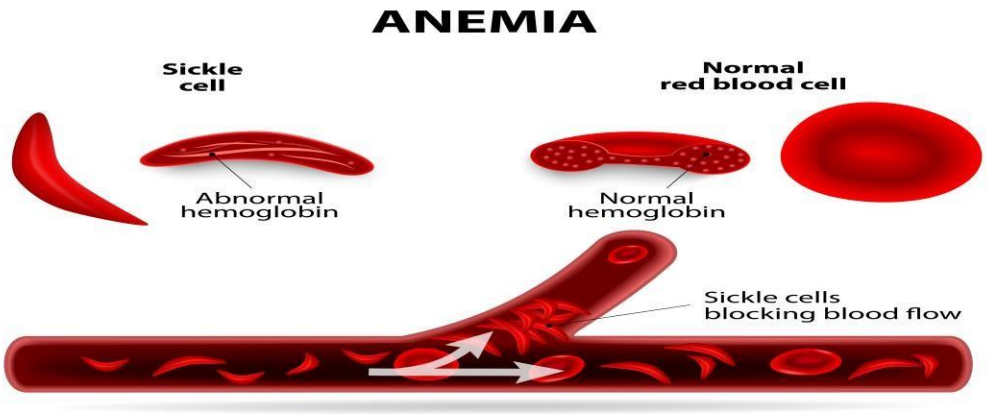
E. SICKLE CELL ANEMIA:

- The term sickle cell disease encompasses a variety of hemoglobinopathies, including sickle cell anemia, sickle Hb C (SC) disease, & sickle cell thalassemia.
- Although the clinical presentations of all are often similar, the manifestations of sickle cell are more severe & so mainly considered.

PATHOPHYSIOLOGY:

- Hb is distinguished as Hb A1, HbA2, Hb C, Hb F & Hb S of which Hb A1, Hb A2 & Hb F are normal.
- Hb A1 – a tetramer consist 2 pairs of globin chains α & β
- Substitution of valine for glutamic acid in both the β chains.
- Each parent contributes a single β chain gene, the heterozygous genotype AS is also possible & is expressed as the sickle cell trait phenotype.
- Deoxygenation in capillaries induces rapid polymerization of the sickling Hb, Hb S & results in formation of helical strands of parallel fibres.
- The elongated, crescent shaped cells characteristic of sickle cell anemia are so produced.

- The affected erythrocytes are rigid & unable to pass through the microvasculature. Vasooclusion with subsequent painful ischemia & chronic organ damage.
- Sickling is reversible upon reexposure to oxygen, however repeated sickling episodes eventually damage the cell membrane.
- The rate of Hb polymerization depends on its concentration in the erythrocyte.
- The co polymerization of Hb S with Hb F inhibits further polymer growth ; intracellular Hb F concentrations are inversely correlated with severity of disease.



CLINICAL PRESENTATIONS

- **Constitutional**

  - Impaired growth & development

  - Increased risk of infection viz meningitis, pneumonia, septicemia

- **Hematologic**

  - Hemolytic anemia

  - Aplastic crises

  - Splenic sequestration crises

- **Vasoocclusive :**

1. Cardiovascular:
- Cardiac enlargement
- Systolic murmur

2. **GI**:
- Autosplenecetomy
- Gallstones / cholecystitis
- Hepatic insufficiency
- Intrahepatic cholelithiais

3. Genitourinary:
- Hematuria
- Impotence
- Priapism
- Renal insufficiency

4. Neurologic :
- Cerebral thrombosis
- Intracerebral hemorrhage
- Seizures
- Subarachnoid haemorrhage

5. Ocular:
- Retinopathy
- Secondary glaucoma

6. Painful crises

7. **Pulmonary**:
- Acute chest syndrome
- Chronic obstructive disease
- Infarction

8. Skin & skeletal :
- Arthropathy
- Aseptic necrosis
- Leg ulcers

DIAGNOSIS:

- Hb electrophoresis → types & proportion of Hb present.
- Is rapid & inexpensive screening test
- It establishes the patients genotype.
- If both parents have the AS genotype there is a 1 in 4 chance that their child will have homozygous SS disease.
- Prenatal diagnosis also possible

TREATMENT:

1. Management of major complications:

a. Anemia

- Blood transfusions
- Folate supplementations

b. Infection

- Cefuroxime for Pneumonia & erythromycin & azithromycin for Mycoplasma pneumonia treatment. Prophylactic penicillin for pneumococcal septicemias.
- Ampicillin & cephalosporins for salmonella infections.

c. Painful crisis

- Vigorous hydration is initiated & oxygen administered if hypoxia is present.
- Ketorolac is given if codeine or oxycodones singly or in combination with acetaminophen are not effective.

2. Management of the sickle cell disease:

a. Transfusion therapy

b. Pharmacologic management : clotrimazole. Pentoxiphylline, antineoplastics, hydroxyurea.

c. Bone marrow transplantation

F. THALASSEMIAS:

- It is an inherited disease.
- Thalassemia is also the hemolytic anemia in which hemoglobin production is decreased.
- The RBCs are small, pale and short lived.
- It required the blood transfusion for life.
- Hemolytic disease of the newborn Rh+ antibodies of a sensitized Rh– mother crossthe placenta and attack and destroy the RBCs of an Rh+ baby.
- Rh– mother becomes sensitized when exposure to Rh+ blood causes her body to synthesize Rh+ antibodies.
- The drug RhoGAM can prevent the Rh– mother from becoming sensitized
- Thalassemias are a group of hereditary disorders of Hb synthesis characterized by impaired production of one or more of the normal polypeptide chains of globin.
- The most prevalent thalassemia syndromes are those that involve diminished or absent synthesis of the α or β globin chains of HbA1.

PATHOPHYSIOLOGY:

- The thalassemia syndromes are collectively one of the most common genetic disorders of the human.
- Reduced production of normal α2 β2 tetramer of HbA1 results in the production of smaller erythrocytes with a low Hb content.
- The synthesis & accumulation of excess normal globin chains within the red cells lead to the formation of unstable aggregates, which may precipitate & cause cell membrane damage
- These deformed cells undergo premature destruction either in the bone marrow (Extravascular hemolysis) or the peripheral circulation (intravascular hemolysis).
- Chronic hemolysis is a primary complication of the clinically significant α & β thalassemia syndromes.(Hb H disease & β thalassemia major).
- The ineffective erythropoiesis & microcytic, hypochromic anemia described earlier are associated with a compensatory ↑ in the absorption of dietary iron.

CLINICAL PRESENTATION:

- This may contribute to the iron overload due to blood transfusion therapy.
- ↑ in erythropoietic activity in the bone marrow& in extramedullary sites.

- In severe form, excessive erythropoiesis causes significant bone marrow hypertrophy, growth retardation, lymphadenopathy & hepatosplenomegaly.
- Bone marrow expansion in untreated patients leads to skeletal deformities & fragility

i. α – THALASSEMIA :

- Four genes are involved in the production of α globin chains, with one pair occurring on each DNA strand (αα/αα).
- The most common form of it result from deletion of one or more of these genes.
- Excess production of β & γ chains result in the formation of unstable & nonfunctional γ4 (Hb Bart's) & β4 (Hb H) tetramers.

Comparison of α-thalassemia syndromes :

Syndrome	**Genotypes**	**Hb conc (g/L)**	**RBC morphology**	**Clinical manifestation**
Silent carrier	-α/αα	150	Normal	None
α-thalassemia trait	-α/-α or -/ αα	120-130	Microcytic	Mild anemia
Hb H disease	-/-α	60-100	Microcytic, deformed	Chronic hemolysis, splenomegaly
Hydrops fetalis	-/-	-	Nucleated RBC	Intrauterine or neonatal death

ii. β-THALASSEMIA:

- It results from faulty mRNA transcription of the β gene.
- Excess of α-chain accumulate & cause membrane damage in RBC precursors.
- So premature destruction of the cells in the bone marrow or peripheral blood.
- α- & δ- chain production is usually unaffected & so ↑ levels of Hb A2 (α2δ2).

Comparison of β-thalassemia syndromes:

Syndrome	**Hb conc (g/L)**	**Clinical manifestation**	**Conventional treatment**
Heterozygous			
Minima	Normal	None	None
Minor (trait)	>100	Mild anemia	Genetic/medical counseling
Homozygous			
Intermedia	70 - 100	Mod – sev anemia, impaired growth & splenomegaly	Intermittent blood transfusion & chelation therapy
Major	20 - 70	Sev anemia, abnormal skeletal growth, splenomegaly, iron load complications	Chronic blood transfusion & chelation therapy

G. HEMOLYTIC ANEMIAS:

- It is caused by an increased rate of RBC destruction.
- It can be because of the production of the defective or damaged RBC's (megaloblastic anemias, thalassemias, sickle cell anemias) or drug induced.

CLASSIFICATION:

1. Inherited:

a. Globin synthesis defect

- Sickle cell anemia
- Thalassemia
- Unstable Hb disease

b. Erythrocyte membrane defect

- Hereditary spherocytosis
- Hereditary elliptocytosis
- Hereditary stomatocytosis

c. Erythrocyte enzyme defect

- HMP shunt defect
- Glycolytic enzyme defect
- Other enzyme defect (adenylate kinase)

2. Acquired

A. Immune mediated

a. Warm reacting Ab (IgG)

- Primary (idiopathic)
- Secondary (collagen vascular disease, lymphoproliferative disorders)
- Drug induced

b. Cold agglutinin disease (IgM)

- Acute (mycoplasma pneumonia, infectious mononucleosis)
- Chronic (lymphoid neoplasms, idiopathic)

c. Paroxysmal nocturnal hemoglobinuria

d. Transfusions reactions

e. Hemolytic disease of newborns

B. Microangiopathic & traumatic

- Disseminated intravascular coagulation
- Hemolytic uremic syndrome
- Thrombotic thrombocytopenic purpura
- Prosthetic or diseased heart valves

C. Infection

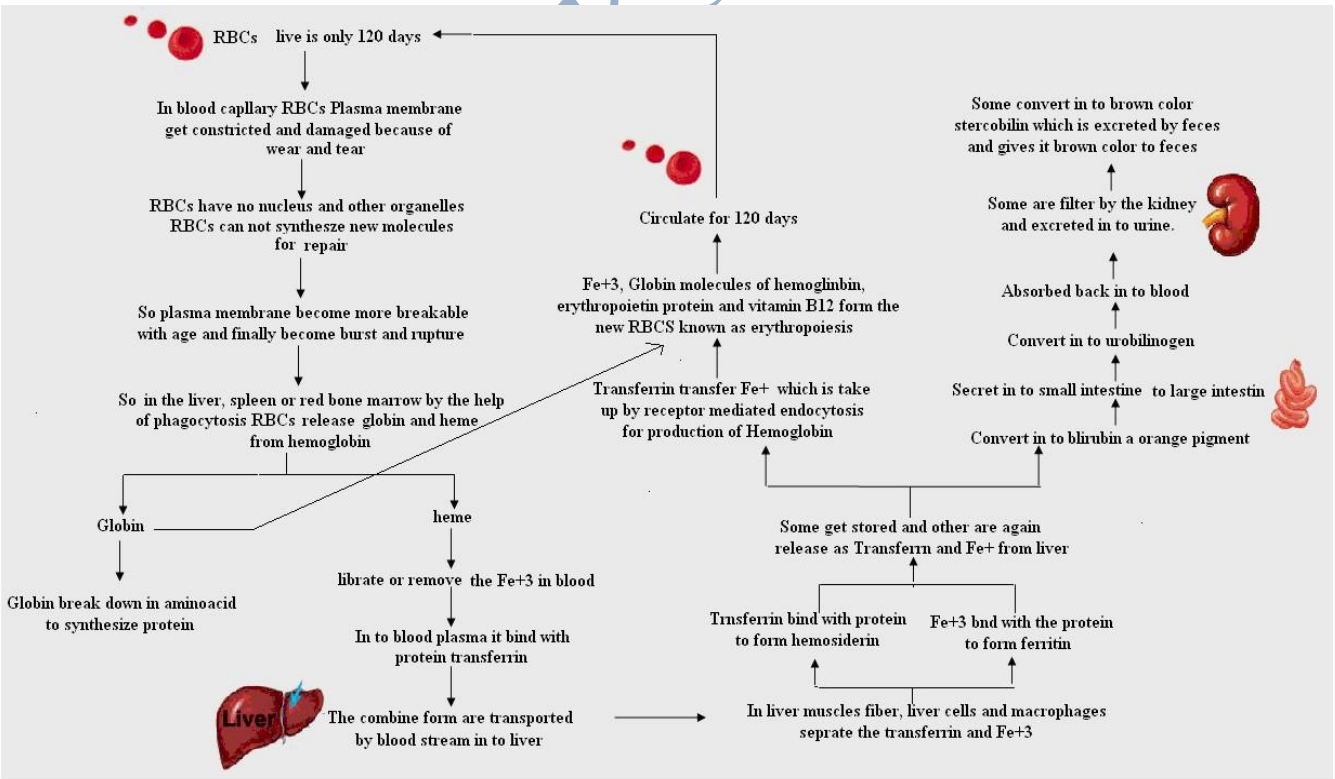
D. Exogenous substances

E. Others

- Liver disease
- Hypophosphatemia

PATHOPHYSIOLOGY:

- It involves hemolysis of RBC within the circulation (intravascular haemolysis) or taken up by the RES & destroyed (extravascular hemolysis).
- Intravascular hemolysis may be caused by trauma to the RBC, complement fixation to the RBC (immune mediated), or exposure to exogenous substances.



- During hemolysis, if haptoglobin binding capacity is exceeded, unbound Hb levels ↑, resulting in hemoglobinemia.
- Free Hb is filtered through the glomerulus & usually is reabsorbed by the proximal tubules.
- In severe intravascular hemolysis, the reabsorptive capacity is exceeded, causing hemoglobinuria.
- Some Hb molecules are transferred from hemopexin to albumin forming methemalbumin.

CLINICAL PRESENTATION & DIAGNOSIS:

	Moderate hemolysis	**Severe hemolysis**
Physical findings		
Jaundice	+	+
Hemoglobinuria	0	+
Laboratory indices: urine		
Hemoglobin	0	+
Hemosiderin	0	+
Laboratory indices: plasma/ serum		
Reticulocytosis	+	++
Plasma Hb	+	++
RBC Hb	Low	Low
Hematocrit	Low	Low
Bilirubin (unconjugated)	+	++
Haptoglobin	Low	Low / -
Hemopexin	Normal / low	Low / -
Methemalbumin	0	+
Lactate dehydrogenase	0	+

I Inherited hemolytic anemia : G6PD deficiency :

- It is the most prevalent inherited RBC enzyme defect, a sex linked (X chromosome) disorder.
- The G6PD enzyme, with glutathione & NADP acts as a protective antioxidant for RBCs against external oxidative stresses.

- In G6PD deficiency, oxidative stresses on the RBC viz drugs, infection or acidosis can lead to denaturation of the globin chains which ppts intracellularly onto the cell membrane as Heinz bodies & premature hemolysis occurs→ oxidative hemolysis.

* **Several factors affecting patient's susceptibility for deficiency:**

- The type of G6PD genetic variant present (i.e. type A- or mediterranean type).
- Patient age
- Other sources of oxidant stress
- Dosage of an offending drugs (nalidixic acid, cephalosporin, nitrofurantoin, etc.)
- Patient metabolism & excretion of offending drugs.

TREATMENT

- Withdrawal or avoidance of any potentially oxidant drugs or other substances.
- In patients with A- variant G6PD deficiency, hemolysis usually is mild & self-limited, so no need of therapy.
- For mediterranean type blood transfusions
- Folic acid supplementation.

II Acquired hemolytic anemia: Autoimmune hemolysis

- Autoimmune hemolytic anemia results from the binding of complement or anti-RBC antibodies to the red cell membrane in affected patients.
- These disorders are classified according to the temperature at which the antibodies have the greatest affinity for & interaction with red cells.

1. Cold agglutinin hemolytic anemia

- Here, IgM antibodies bind to RBCs at low temperatures (4° C).
- This agglutination process is reversed quickly during warming.
- Most don't appreciably shorten RBC survival.
- It is associated with mycoplasma pneumonia or infectious mononucleosis.
- Chronic disease occurs with lymphoproliferative disorders & results in poor peripheral circulation.
- It involves preventing exposure to cold environments.
- Folic acid supplementation
- Blood transfusions (if necessary)

- Treating any underlying diseases.
- Occasssionaly patients may respond to plasmapheresis or cytotoxic agents such as cyclophosphamide or chlorambucil

2. Warm autoimmune hemolytic anemia :

- IgG or occasionally IgA have greatest affinity for red cells at room temperature (37°C).
- Hemolysis involves the attachment & subsequent destruction of IgG coated erythrocytes to receptors on macrophages in the RES.
- It may be idiopathic, secondary to an underlying disease that affects immune system (chronic lymphocytic leukemia, non Hodgkins lymphoma, or systemic lupus erythematosus), or secondary to certain drugs.
- When hemolysis is clinically significant, corticosteroid therapy is effective & blood transfusions may be needed.
- Splenectomy
- Alternative therapies include immunosuppressive agents, danazol, IVIG & cyclosporine

CENTRAL NERVOUS SYSTEM

The skull and the vertebrae form a rigid compartment encasing the delicate brain and spinal cord. The average weight of the brain is about 1400 gm in men and 1250 gm in women. There are 2 types of tissues in the nervous system:

1. ***Neuroectodermal tissues*** which include neurons (nerve cells) and neuroglia, and together form the predominant constituent of the CNS.

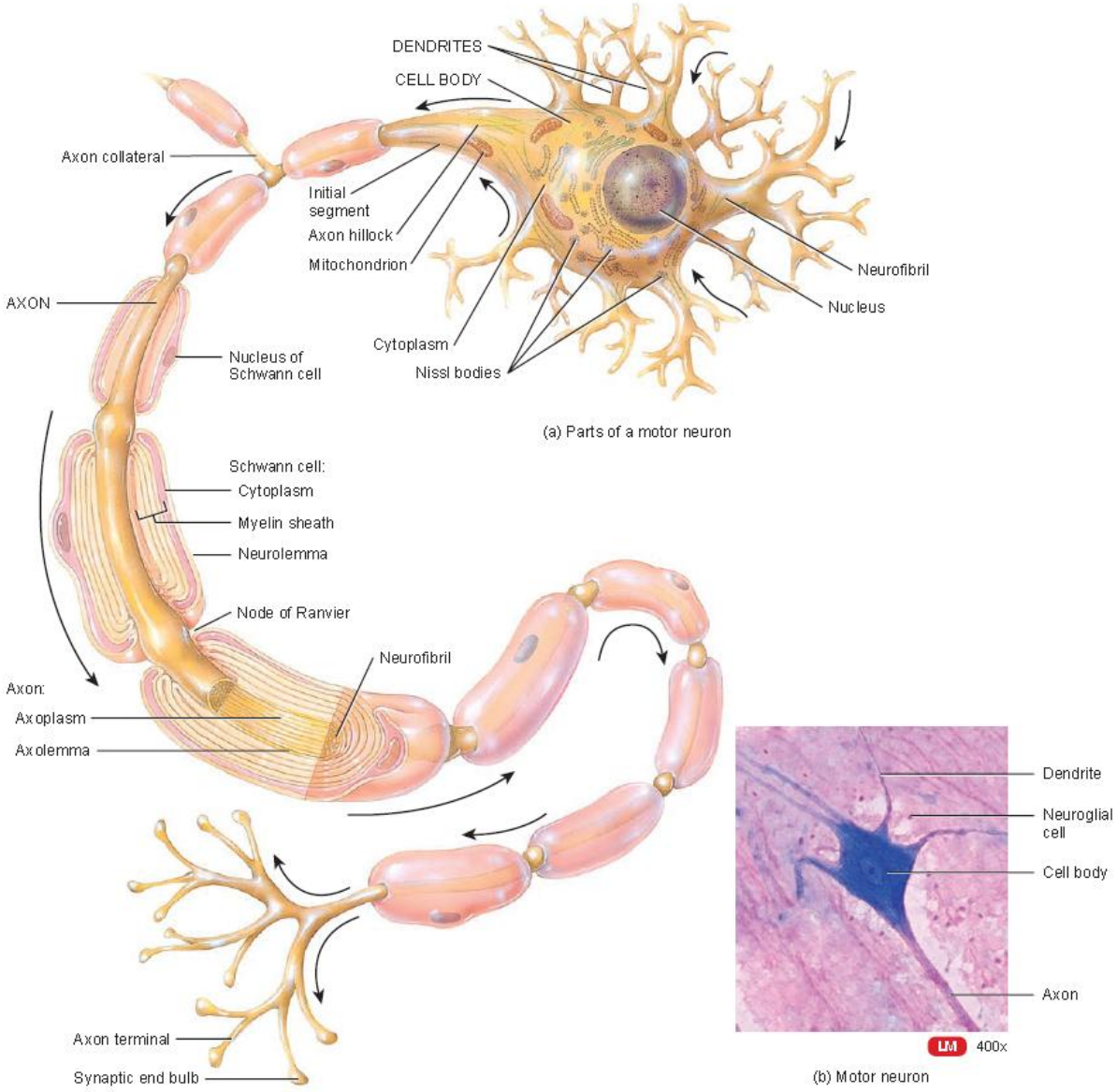
2. ***Mesodermal tissues*** are microglia, dura mater, the leptomeninges (pia-arachnoid), blood vessels and their accompanying mesenchymal cells.

The predominant tissues comprising the nervous system and their general response to injury are briefly considered below:

1. NEURONS The neurons are highly specialised cells of the body which are incapable of dividing after the first few weeks of birth. Thus, brain damage involving the neurons is irreversible. Neurons vary considerably in size and shape. A neuron consists of 3 main parts: the cell body, an axon and numerous dendrites.

1) **The cell body**: The cell body contains a nucleus surrounded by cytoplasm that includes typical cellular organelles such as lysosomes, mitochondria, ribosomes, endoplasmic reticulum and a Golgi complex. A cluster of neuronal cell bodies located in the PNS is called ganglion (plural is ganglia) and a cluster of neuronal cell bodies located in the CNS is called nucleus (plural is nuclei).
2) **Dendrites**: Dendrites (little trees) are the receiving or input portions of a neuron. They usually are short, tapering, and highly branched and form a tree-shaped array of processes extending from the cell body.
3) **Axon:** An axon is a long, thin, cylindrical projection that carries nerve impulse to other neuron, muscle or glands. It is often joint to the cell body at a cone-shaped elevation called the axon hillock (small hill). The part of the axon closest to the axon hillock is the initial segment. In most neurons, nerve impulses arise at the junction of the axon hillock and the initial segment, an area called the trigger zone, from which they travel along the axon to their destination. The axon of a neuron propagates nerve impulses toward another neuron, a muscle fiber, or a gland cell. Axon can have side branches (at right angle to axon) which are called **axon collaterals**. At the ends, the axon divide into many fine processes called **axon terminals (telodendria)**. The tips of axon terminals swell into bulb-shaped structures called **synaptic end bulbs**. Synaptic end bulbs contain many tiny membrane-enclosed sacs called synaptic vesicles that store a chemical **neurotransmitter**. Many neurons contain two or even three types of neurotransmitters, each with different effects on the postsynaptic

cell. When neurotransmitter molecules are released from synaptic vesicles, they excite or inhibit other neurons, muscle fibers, or gland cells. The site of communication between two neurons or between a neuron and an effector cell is called a **synapse**. Bundle of axons located in the PNS is called a Nerve. Cranial nerves connect the brain to the periphery, whereas spinal nerves connect the spinal cord to the periphery. A bundle of axons located in the CNS is called Tract. Tracts interconnect neurons in the spinal cord and brain.



2. NEUROGLIA The neuroglia provides supportive matrix and maintenance to the neurons. It includes 3 types of cells: astrocytes, oligodendrocytes and ependymal cells.

i) Astrocytes The astrocytes are stellate cells with numerous fine branching processes. An astrocyte has round or oval vesicular nucleus, but unlike neuron, lacks a prominent nucleolus.

The main *functions* of astrocytes in health are physiological and biochemical support to the neurons and interactions with capillary endothelial cells which establishes blood brain barrier. In case of damage to the brain, astrocytes act like fibroblasts of other tissues. The astrocytes in response to injury undergo hyperplasia and hypertrophy termed 'gliosis'.

ii) Oligodendrocytes Oligodendrocytes are so named because of their short and fewer processes when examined by light microscopy with special stains (*oligo*=short). The major *function* of oligodendrocytes is formation and maintenance of myelin. Thus, in this respect they are counterparts of Schwann cells of the peripheral nervous system.

iii) Ependymal cells The ependymal cells are epitheliumlike and form a single layer of cells lining the ventricular system, aqueduct, central canal of the spinal cord and cover the choroid plexus. The ependymal cells influence the formation and composition of the cerebrospinal fluid (CSF) by processes of active secretion, diffusion, absorption and exchange.

3. MICROGLIA

Microglia is the nervous system counterpart of the monocyte-macrophage system. Although the term 'microglia' is commonly used but it is inappropriate since these cells, unlike neuroglia, are not of neuroectodermal origin. Microglial cells (or Hortega cells) are not fixed but are mobile cells. These cells are found throughout the brain and are often present close to the blood vessels. Normally, microglial cells appear as small inconspicuous cells with bean-shaped vesicular nuclei, scanty cytoplasm and long cytoplasmic processes. In response to injury or damage, however, these cells have capability to enlarge in size, proliferate and develop elongated nuclei, so called *rod cells*. Microglial cells may actually assume the shape and phagocytic function of macrophages.

4. DURA MATER

The dura mater is a tough fibrous covering of the brain which is closely attached to the skull on its inner layer of endocranial periosteum. In the region of spinal canal, it encloses a potential space, the *epidural space,* between the bone and the dura. The dura is composed of dense collagen, fused with periosteum of the skull.

5. PIA-ARACHNOID (LEPTOMENINGES)

The leptomeninges (*lepto*=thin, slender) consisting of the pia and arachnoid mater form the delicate vascular membranous covering of the central nervous system. The pia mater is closely applied to the brain and its convolutions, while the arachnoid mater lies between the pia mater and the dura mater without dipping into sulci. Thus, a space is left between the two layers of leptomeninges, known as *subarachnoid space,* which contains the CSF. The major arteries and veins run in the subarachnoid space and small nutrient arteries pass into the cortex.

EPILEPSY

Epilepsy is a disorder that is best viewed as a symptom of disturbed electrical activity in the brain caused by a wide variety of etiologies. It is a collection of many different types of seizures that vary widely in severity, appearance, cause, consequence, and management.

Epilepsy implies a periodic recurrence of seizures with or without convulsions. Seizures that are prolonged or repetitive can be life-threatening. The effect epilepsy has on patients' lives can be extremely frustrating.

ETIOLOGY

Seizures occur because small numbers of neurons discharge abnormally. Anything that disrupts the normal homeostasis of the neuron and disturbs its stability may trigger abnormal activity and seizures. Patients with mental retardation and cerebral palsy are at increased risk for seizures.

In the elderly, seizures are primarily partial in onset. The causes of seizures in the elderly may be multifactorial and include cerebrovascular disease (both ischemic and hemorrhagic stroke), neurodegenerative disorders, tumor, head trauma, metabolic disorders, and CNS infections. In many cases, patients will present with seizures that do not have an identifiable cause and thus have idiopathic epilepsy.

Many factors have been shown to precipitate seizures in susceptible individuals. Hyperventilation may precipitate absence seizures. Sleep, sleep deprivation, sensory stimuli, and emotional stress may initiate seizures. Hormonal changes occurring around the time of menses, puberty, or pregnancy have been associated with the onset of or an increased frequency of seizures.

PATHOPHYSIOLOGY

Seizure activity is characterized by paroxysmal discharges occurring synchronously in a large population of cortical neurons. This is characterized on EEG as a sharp wave or *spike.*

The basic physiology of a seizure episode is traceable to an unstable cell membrane or its surrounding supportive cells. The seizure originates from the gray matter of any cortical or perhaps subcortical area. Initially, a small number of neurons fire abnormally. Normal membrane conductances and inhibitory synaptic currents break down, and excess excitability spreads, either locally to produce a focal seizure or more widely to produce a generalized seizure. The clinical manifestations depend on the site of the focus, the degree of irritability of the surrounding area of the brain, and the intensity of the impulse.4

An abnormality of potassium conductance, a defect in the voltage-sensitive ion channels, or a deficiency in the membrane ATPases linked to ion transport may result in

neuronal membrane instability and a seizure. Selected neurotransmitters (e.g., glutamate, aspartate, acetylcholine, norepinephrine, histamine, corticotropinreleasing factor, purines, peptides, cytokines, and steroid hormones) enhance the excitability and propagation of neuronal activity, whereas *γ* -aminobutyric acid (GABA) and dopamine inhibit neuronal activity and propagation. A relative deficiency of inhibitory neurotransmitters such as GABA or an increase in excitatory neurotransmitters such as glutamate would promote abnormal neuronal activity. Normal neuronal activity also depends on an adequate supply of glucose, oxygen, sodium, potassium, chloride, calcium, and amino acids. Systemic Ph is also a factor in precipitating seizures.

During a seizure, there is a large increase in the demand for blood flow to the brain to carry off CO_2 and to bring substrates for neuronal metabolic activity. The more prolonged the seizure, the more likely the brain is to suffer ischemia that may result in neuronal destruction and brain damage. Also, the continued exposure to glutamate, an excitatory neurotransmitter, may contirubte to neuronal damage.

Types of Seizures

Partial seizures with an alteration of consciousness are described as *complex partial.* With complex partial seizures, the patient may have automatisms, periods of memory loss, or aberrations of behavior.

Generalized seizures have clinical manifestations that indicate involvement of both hemispheres. Motor manifestations are bilateral, and there is a loss of consciousness.

Generalised Tonic Clonic seizures are what many people think of as epilepsy. The seizure results in a sudden sharp tonic contraction of muscles followed by a period of rigidity and clonic movements. During the seizure, the patient may cry or moan, lose sphincter control, bite the tongue, or develop cyanosis. After the seizure, the patient may have altered conciousness, drowsiness, or confusion for a variable period of time (postictal period) and frequently goes into a deep sleep. Tonic and clonic seizures may occur separately.

Brief shock like muscular contractions of the face, trunk, and extremities are known as ***myoclonic jerks***. They may be isolated events or rapidly repetitive. A sudden loss of muscle tone is known as an ***atonic seizure***.

TABLE 54–1. International Classification of Epileptic Seizures

I. Partial seizures (seizures begin locally)
  A. Simple (without impairment of consciousness)
    1. With motor symptoms
    2. With special sensory or somatosensory symptoms
    3. With psychic symptoms
  B. Complex (with impairment of consciousness)
    1. Simple partial onset followed by impairment of consciousness—with or without automatisms
    2. Impaired consciousness at onset—with or without automatisms
  C. Secondarily generalized (partial onset evolving to generalized tonic-clonic seizures)
II. Generalized seizures (bilaterally symmetrical and without local onset)
  A. Absence
  B. Myoclonic
  C. Clonic
  D. Tonic
  E. Tonic-clonic
  F. Atonic
  G. Infantile spasms
III. Unclassified seizures
IV. Status epilepticus

PARKINSON'S DISEASE

Parkinson's disease is a progressive nervous system disorder that affects movement. Symptoms start gradually, sometimes starting with a barely noticeable tremor in just one hand. Tremors are common, but the disorder also commonly causes stiffness or slowing of movement.

In the early stages of Parkinson's disease, your face may show little or no expression. Your arms may not swing when you walk. Your speech may become soft or slurred. Parkinson's disease symptoms worsen as your condition progresses over time.

Although Parkinson's disease can't be cured, medications might significantly improve your symptoms. Occasionally, your doctor may suggest surgery to regulate certain regions of your brain and improve your symptoms.

ETIOLOGY

In Parkinson's disease, certain nerve cells (neurons) in the brain gradually break down or die. Many of the symptoms are due to a loss of neurons that produce a chemical messenger in your brain called dopamine. When dopamine levels decrease, it causes abnormal brain activity, leading to symptoms of Parkinson's disease.

The cause of Parkinson's disease is unknown, but several factors appear to play a role, including:

- **Your genes.** Researchers have identified specific genetic mutations that can cause Parkinson's disease. But these are uncommon except in rare cases with many family members affected by Parkinson's disease.

  However, certain gene variations appear to increase the risk of Parkinson's disease but with a relatively small risk of Parkinson's disease for each of these genetic markers.

- **Environmental triggers.** Exposure to certain toxins or environmental factors may increase the risk of later Parkinson's disease, but the risk is relatively small.

Researchers have also noted that many changes occur in the brains of people with Parkinson's disease, although it's not clear why these changes occur. These changes include:

- **The presence of Lewy bodies.** Clumps of specific substances within brain cells are microscopic markers of Parkinson's disease. These are called Lewy bodies, and

researchers believe these Lewy bodies hold an important clue to the cause of Parkinson's disease.

- **Alpha-synuclein is found within Lewy bodies.** Although many substances are found within Lewy bodies, scientists believe an important one is the natural and widespread protein called alpha-synuclein (a-synuclein). It's found in all Lewy bodies in a clumped form that cells can't break down. This is currently an important focus among Parkinson's disease researchers.

PATHOPHYSIOLOGY:

The **pathophysiology of Parkinson's disease** is death of dopaminergic neurons as a result of changes in biological activity in the brain with respect to Parkinson's disease (PD). There are several proposed mechanisms for neuronal death in PD; however, not all of them are well understood. Five proposed major mechanisms for neuronal death in Parkinson's Disease include protein aggregation in Lewy bodies, disruption of autophagy, changes in cell metabolism or mitochondrial function, neuroinflammation, and blood-brain barrier (BBB) breakdown resulting in vascular leakiness.

PROTEIN AGGREGATION

The first major proposed cause of neuronal death in Parkinson's disease is the bundling, or oligomerization, of proteins. The protein alpha-synuclein has increased presence in the brains of Parkinson's Disease patients and, as α-synuclein is insoluble, it aggregates to form Lewy bodies (shown to left) in neurons. Lewy bodies first appear in the olfactory bulb, medulla oblongata, and pontine tegmentum; patients at this stage are asymptomatic. As the disease progresses, Lewy bodies develop in the substantia nigra, areas of the midbrain and basal forebrain, and in the neocortex.

DISRUPTION OF AUTOPHAGY

The second major proposed mechanism for neuronal death in Parkinson's disease, autophagy, is a mechanism by which inner components of the cell are broken down and recycled for use. Autophagy has been shown to play a role in brain health, helping to regulate cellular function. Disruption of the autophagy mechanism can lead to several different types of diseases like Parkinson's disease.

CHANGES IN CELL METABOLISM OR MITOCHONDRIAL FUNCTION

The third major proposed cause of cell death in Parkinson's disease involves the energy-generating mitochondrion organelle. In Parkinson's disease, mitochondrial function is disrupted, inhibiting energy production and resulting in death.

The mechanism behind mitochondrial dysfunction in Parkinson's disease is hypothesized to be the **PINK1 and Parkin** complex, having been shown to drive autophagy of mitochondria (also known as mitophagy). **PINK1** is a protein normally transported into the mitochondrion, but can also accumulate on the surface of impaired mitochondria. Accumulated PINK1 then recruits Parkin; Parkin initiates the breakdown of dysfunctional mitochondria, a mechanism that acts as a "quality control". In Parkinson's disease, the genes coding PINK1 and Parkin are thought to be mutated, therefore preventing the breakdown of impaired mitochondria, causing abnormal function and morphology of mitochondria and eventually cell death.

Another mitochondrial-related mechanism for cell death in Parkinson's disease is the generation of reactive oxygen species (ROS). ROS are highly reactive molecules that contain oxygen and can disrupt functions within the mitochondria and the rest of the cell. With increasing age, mitochondria lose their ability to remove ROS yet still maintain their production of ROS, causing an increase in net production of ROS and eventually cell death.

NEUROINFLAMMATION

The fourth proposed major mechanism of neuronal death in Parkinson's disease, neuroinflammation, is generally understood for neurodegenerative diseases, however, specific mechanisms are not completely characterized for PD. One major cell type involved in neuroinflammation is the microglia.

BLOOD-BRAIN BARRIER (BBB) BREAKDOWN

The fifth proposed major mechanism for cell death is the breakdown of the blood-brain barrier (BBB). The BBB has three cell types which tightly regulate the flow of molecules in and out of the brain: endothelial cells, pericytes, and astrocytes. In neurodegenerative diseases, BBB breakdown has been measured and identified in specific regions of the brain, including the substantia nigra in Parkinson's disease and hippocampus in Alzheimer's disease.

ALZHEIMER'S DISEASE

Alzheimer's disease (AD), first characterized by Alois Alzheimer in 1907, is a gradually progressive dementia affecting both cognition and behavior.

AD is the most common cause of dementia, accounting for over 60% of cases of late-life cognitive dysfunction. Approximately 4.5 million Americans have AD. By the year 2050, one of five people will be over age 65 years, and the number of AD patients is projected to be 13.2 million. AD is generally associated with the elderly because most cases present in persons older than age 65, but in about 5% of cases onset can be as early as age 40, resulting in the arbitrary age classifications of earlyonset (ages 40 to 64 years) and late-onset (age 65 years and older).

ETIOLOGY

GENETICS

Genetic factors have been investigated in both early- and late onset AD. Almost all early-onset cases of AD can be attributed to alterations on **chromosomes 1, 14, or 21**. The majority and most aggressive early-onset cases are attributed to mutations of an Alzheimer's gene located on chromosome 14, which produces a protein called presenilin 1. Similar in structure to presenilin 1 is a protein produced by a gene on chromosome 1 called presenilin 2. Presenilin 2 is responsible for early-onset AD. It has been suggested, but not proven, that presenilins are either γ -secretase or that presenilins affect γ –secretase activity. APP is encoded on chromosome 21. Only a small number of early-onset familial AD cases have been associated with mutations in the APP gene, resulting in overproduction of beta-amyloid protein (βAP).

Genetic susceptibility to late-onset AD is thought to be primarily influenced by the apolipoprotein E (apo E) genotype. The gene responsible for the production of apo E is located on chromosome 19 in a region previously associated with late-onset AD.

ENVIRONMENTAL AND OTHER FACTORS

A number of environmental factors have been associated with an increased risk of AD, including stroke, alcohol abuse, small head circumference, repeated or severe head trauma, Down syndrome, and lower levels of education. In particular, traumatic head injury in combination with the apo E4 genotype has been associated with an increased risk of AD.

PATHOPHYSIOLOGY

STRUCTURAL CHANGES

AD is defined by both neuropathologic and clinical criteria. Neuropathologically, AD destroys neurons in the cortex and limbic structures of the brain, particularly the basal forebrain,

amygdala, hippocampus, and cerebral cortex. These areas are responsible for higher learning, memory, reasoning, behavior, and emotional control.

Anatomically, four major alterations in brain structure are seen: cortical atrophy, degeneration of cholinergic and other neurons, presence of neurofibrillary tangles (NFTs), and the accumulation of neuritic plaques.

- NFTs are comprised of paired helical filaments that aggregate in dense bundles. Paired helical filaments are formed from tau protein. Tau protein provides structural support to microtubules, the cell's transportation and skeletal support system. When tau filaments undergo abnormal phosphorylation at a specific site, they cannot bind effectively to microtubules, and the microtubules collapse. Without an intact system of microtubules, the cell cannot function properly and eventually dies. Overactivity of kinases such as microtubule affinity-regulating kinase, or underactivity of phosphatases could theoretically produce or prevent breakdown of abnormally phosphorylated tau protein.
- Neuritic plaques (also termed amyloid or senile plaques) are extracellular lesions found in the brain and cerebral vasculature. Plaques are comprised of *β*AP, and an entwined mass of broken neurites (axon and dendrite projections of neurons). Two types of glial cells, astrocytes and microglia, are also found in plaques. Among other functions, glial cells secrete inflammatory mediators and serve as scavenger cells, which may be important in causing the inflammatory processes that occur in the development of AD.

Formation of Neuritic plaques: Forming the centre of the neuritic plaque are aggregates of a 39- to 43-amino acid protein segment called *β*AP. The *β*AP accumulating in the brain and cerebral blood vessels in AD is different from other disease-producing amyloid proteins.7 *β*AP is cleaved from the APP, a transmembrane protein. Proteases cleave APP in several different ways. In the normal secretory pathway APP is cleaved through the *β*AP region, first using an enzyme called *α*-secretase, and then by an enzyme termed *γ* -secretase. The resulting product, p3, is soluble and harmless. In the potentially pathologic process, the endosomal pathway cleaves on both sides of *β*AP, first with *β*-secretase and then with *γ* -secretase, resulting in the formation of a *β*AP fragment which is released into the extracellular space.

Effect of Neuritic Plaque: Although it is not known how *β*AP causes neuronal damage, it does cause dysregulation in calcium and damage to mitochondria. This in turn may trigger inflammatory mediators.

INFLAMMATORY MEDIATORS

Inflammatory mediators and other immune system constituents are present near areas of plaque formation, suggesting that the immune system plays an active role in the pathogenesis of AD. Microglial cells located around and within amyloid plaques are thought to release

inflammatory mediators, which locally destroy neuronal tissue. Glial cells also function as phagocytes, similar to macrophages and monocytes in the periphery.

THE CHOLINERGIC SYSTEM

Multiple neuronal pathways are destroyed in AD. Damage occurs in any nerve cell population located in or traveling through plaque-laden areas. Most profoundly damaged are the cholinergic pathways, particularly a large system of neurons located at the base of the forebrain in the nucleus basalis of Meynert, a brain area believed to be involved in thought integration. Axons of these cholinergic neurons project to the frontal cortex and hippocampus, areas strongly associated with memory and cognition.

CLINICAL PRESENTATION

The onset of AD is almost imperceptible, without abrupt changes in cognition or function. Deficits occur progressively over time, affecting multiple areas of cognition.

SCHIZOPHRENIA

Schizophrenia is one of the most complex and challenging of psychiatric disorders. It represents a heterogeneous syndrome of disorganized and bizarre thoughts, delusions, hallucinations, inappropriate affect, and impaired psychosocial functioning.

The U.S. lifetime prevalence of schizophrenia ranges from 0.6% to 1.9%, with an average of approximately 1%. With only a few possible exceptions, the worldwide prevalence of schizophrenia is remarkably similar among all cultures. Schizophrenia most commonly has its onset in late adolescence or early adulthood and rarely occurs before adolescence or after the age of 40 years. Although the prevalence of schizophrenia is equal in males and females, the onset of illness tends to be earlier in males.

ETIOLOGY

Although the etiology of schizophrenia is unknown, research has demonstrated various abnormalities in brain structure and function. The cause of schizophrenia is likely multifactorial; that is, multiple pathophysiologic abnormalities may play a role in producing the similar but varying clinical phenotypes we refer to as schizophrenia.

- A neurodevelopmental model has been evoked as one possible explanation for the etiology of schizophrenia. This model proposes that schizophrenia has its origins in some as yet unknown in utero disturbance, possibly occurring during the second trimester of pregnancy. This “schizophrenic lesion” may result in abnormalities in cell shape, position, symmetry, and connectivity, and functionally to the development of abnormal brain circuits. Some studies associate upper respiratory infections during the second trimester of pregnancy with a higher incidence of schizophrenia. Other studies show a relationship between obstetric complications or neonatal hypoxia and schizophrenia. Some studies also associate low birth-weight (<2,500 g) with schizophrenia.
- Additional support for a developmental model is provided by the fact that although studies have shown decreased cortical thickness and increased ventricular size in the brains of many patients with schizophrenia, this occurs in the absence of widespread gliosis.3 Gliosis, or the proliferation of glial cells, is thought to occur as a compensatory change in degenerative diseases of the brain.
- Although a specific abnormality has not been discovered, increasing evidence suggests a genetic basis for schizophrenia. Although the risk of developing schizophrenia is 0.6% to 1.9% in the general population, this increases to approximately 10% if a first-degree relative has the illness and to 3% if a second-degree relative has the illness.

PATHOPHYSIOLOGY

NEUROTRANSMITTER CHANGES

- Dopamine dysfunction

The first formulations of the dopamine hypothesis of schizophrenia came from post-mortem studies finding increased striatal availability of D_2/D_3 receptors in the striatum, as well as studies finding elevated CSF levels of dopamine metabolites. Subsequently, most antipsychotics were found to have affinity for D_2 receptors. More modern investigations of the hypothesis suggest a link between striatal dopamine synthesis and positive symptoms, as well as increased and decreased dopamine transmission in subcortical and cortical regions respectively.

Exactly how dopamine dysregulation can contribute to schizophrenia symptoms remains unclear. Some studies have suggested that disruption of the auditory thalamocortical projections give rise to hallucinations, while dysregulated corticostriatal circuitry and reward circuitry in the form of aberrant salience can give rise to delusions. Decreased inhibitory dopamine signals in the thalamus have been hypothesized to result in reduced sensory gating, and excessive activity in excitatory inputs into the cortex.

- Glutamate abnormalities

Beside the dopamine hypothesis, interest has also focused on the neurotransmitter glutamate and the reduced function of the NMDA glutamate receptor in the pathophysiology of schizophrenia. This has largely been suggested by lower levels of glutamate receptors found in post-mortem brains of people previously diagnosed with schizophrenia and the discovery that glutamate blocking drugs such as phencyclidine and ketamine can mimic the symptoms and cognitive problems associated with the condition.

The fact that reduced glutamate function is linked to poor performance on tests requiring frontal lobe and hippocampal function and that glutamate can affect dopamine function, all of which have been implicated in schizophrenia, have suggested an important mediating (and possibly causal) role of glutamate pathways in schizophrenia.

- Serotonin Dysfunction:

Serotoninergic receptors are present on dopaminergic axons, and it is known that stimulation of these receptors will decrease DA release, at least in the striatum. Patients with schizophrenia with abnormal brain scans have higher whole-blood 5-HT concentrations, and these concentrations are correlated with increased ventricular size. Atypical antipsychotics with potent 5-HT_2 receptor antagonist effects reverse worsening of symptomatology induced by 5-HT agonists in patients with schizophrenia.

CLINICAL PRESENTATION

Schizophrenia is the most common functional psychosis, and there are as many clinical presentations of schizophrenia as there are individuals with the disorder. Schizophrenia is a chronic disorder of thought and affect with the individual having a significant disturbance in interpersonal relationships and ability to function in society on a daily basis.

DEPRESSIVE DISORDERS

Major depressive disorder is a disorder of mood in which the individual experiences one or more major depressive episodes without a history of manic, mixed, or hypomanic episodes. Depression is associated with significant functional disability, morbidity, and mortality.

ETIOLOGY

The etiology of depressive disorders is too complex to be totally explained by a single social, developmental, or biologic theory. Several factors appear to work together to cause or precipitate depressive disorders. The symptoms reported by patients with major depression consistently reflect changes in brain monoamine neurotransmitters, specifically norepinephrine (NE), serotonin (5-HT), and dopamine (DA).

PATHOPHYSIOLOGY

Monoamine hypothesis

Considering the origin of the noradrenergic, serotonergic, and dopaminergic neurones in the brain and their projections into many areas of the brain, it is clear that monoaminergic systems are responsible for many behavioural symptoms, such as mood, vigilance, motivation, fatigue, and psychomotor agitation or retardation. Abnormal function and the behavioural consequences of either depression or the manic state may arise from altered synthesis, storage, or release of the neurotransmitters, as well as from disturbed sensitivity of their receptors or subcellular messenger functions.

The first major hypothesis of depression was formulated about 30 years ago and proposed that the main symptoms of depression are due to a functional deficiency of the brain monoaminergic transmitters norepinephrine (NE), 5-HT, and/or dopamine (DA), whereas mania is caused by functional excess of monoamines at critical synapses in the brain. Evidence for this hypothesis came from clinical observations and animal experiments, which showed that the antihypertensive drug reserpine, which causes a depletion of presynaptic stores of NE, 5-HT, and DA, induced a syndrome resembling depression.

CLINICAL PRESENTATION

- EMOTIONAL SYMPTOMS:

A major depressive episode is characterized by a persistent, diminished ability to experience pleasure.
A loss of interest and pleasure in usual activities, hobbies, or work is common.

Patients appear sad or depressed, and they are often pessimistic and believe that nothing will help them feel better.

The presence of intense hopelessness and complete or near-total loss of interest and pleasure in usual activities may identify patients at risk for suicide.

Patients often have guilt feelings that are unrealistic, and these may reach delusional proportions. Patients may feel that they deserve punishment and may view their present illness as a punishment.

- PHYSICAL SYMPTOMS

Chronic fatigue is a common complaint, with a decreased ability to perform normal daily tasks. Fatigue often appears worse in the morning and does not improve with rest.

Sleep disturbances generally present as frequent early morning awakening (terminal insomnia), with difficulty returning to sleep.

Appetite disturbances, including complaints of decreased appetite, often result in substantial weight loss, especially in the elderly.

Some patients exhibit gastrointestinal complaints, others cardiovascular complaints, especially palpitations. Patients frequently present with a loss of sexual interest or libido.

THE ENDOCRINE SYSTEM

Anatomically, the endocrine system consists of 6 distinct organs: pituitary, adrenals, thyroid, parathyroids, gonads, and pancreatic islets. Understanding the pathology of these endocrine organs requires the knowledge of overall framework of hormone secretions, their actions and broad principles of feedback mechanisms.

Broadly speaking, human hormones are divided into 5 major classes which are further grouped under two headings depending upon their site of interactions on the target cell receptors.

Group I: Those interacting with cell-surface membrane receptors:

1. *Amino acid derivatives:* thyroid hormone, catecholamines.
2. *Small neuropeptides:* gonadotropin-releasing hormone (GnRH), thyrotropin-releasing hormone (TRH), somatostatin, vasopressin.

Group II: Those interacting with intracellular nuclear receptors:

3. *Large proteins:* insulin, luteinising hormone (LH), parathormone hormone.
4. *Steroid hormones:* cortisol, oestrogen.
5. *Vitamin derivatives:* retinol (vitamin A) and vitamin D.

Major functions of hormones are as under:

i) ***Growth and differentiation of cells****:* by pituitary hormones, thyroid, parathyroid, steroid hormones.

ii) ***Maintenance of homeostasis****:* by thyroid (by regulating BMR), parathormone, mineralocorticoids, vasopressin, and insulin.

iii) ***Reproduction:*** sexual development and activity, pregnancy, foetal development, menopause etc.

Regulation of secretion:

A basic feature of all endocrine glands is the existence of both negative and positive **feedback control system** that *stimulates* or *regulates* hormone production in a way that levels remain within the normal range. The stimulatory or regulatory action by endocrine hormonal secretions may follow paracrine or autocrine pathways:

- *Paracrine regulation* means that the stimulatory/regulatory factors are released by one type of cells but act on another adjacent cell of the system.
- *Autocrine regulation* refers to action of the factor on the same cell that produced it.

With this brief overview of principles of physiology of hormones, we now turn to the study of diseases of the endocrine organs. In general, pathologic processes affecting endocrine glands with resultant hormonal abnormalities may occur from following processes:

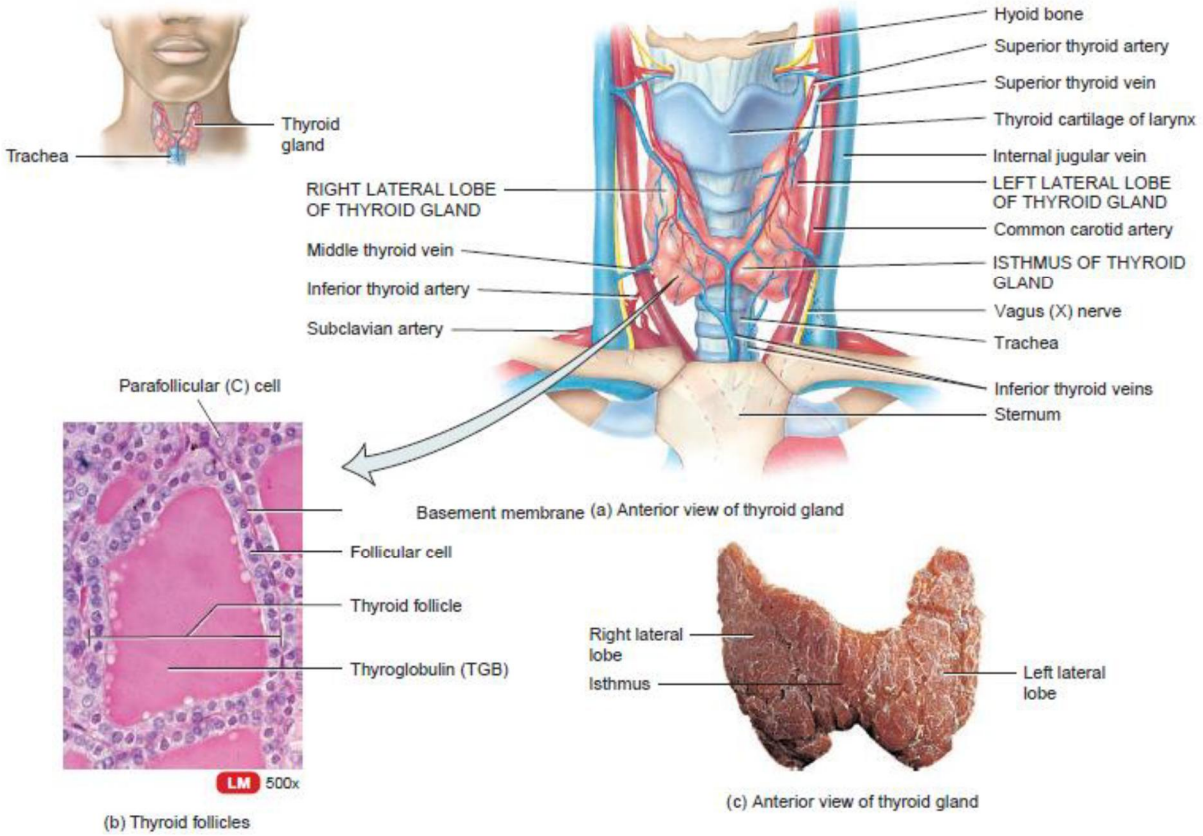
Hyperfunction This results from excess of hormone secreting tissues e.g. hyperplasia, tumours (adenoma, carcinoma), ectopic hormone production, excessive stimulation from inflammation (often autoimmune), infections, iatrogenic (drugs-induced, hormonal administration).

Hypofunction Deficiency of hormones occurs from destruction of hormone-forming tissues from inflammation (often autoimmune), infections, iatrogenic (e.g. surgical removal, radiation damage), developmental defects (e.g. Turner's syndrome, hypoplasia), enzyme deficiency, haemorrhage and infarction (e.g. Sheehan's syndrome), nutritional deficiency (e.g. iodine deficiency).

Hormone resistance There may be adequate or excessive production of a hormone but there is peripheral resistance, often from inherited mutations in receptors (e.g. defect in membrane receptors, nuclear receptors or receptor for signal transduction).

THYROID GLAND

It is a butterfly-shaped gland which is located just inferior to the larynx (voice box). It is composed of right and left lateral lobes that are connected by isthmus (a narrow passage). It is highly vascularized and receives 80–120 mL of blood per minute. Thyroid gland is made up of microscopic spherical sacs called thyroid follicles. The wall of each follicle consists of follicular cells which produce two hormones: thyroxine (tetraiodothyronine or T4 because it contains four atoms of iodine) and triiodothyronine (T3, which contains three atoms of iodine). T3 and T4 together are also known as **thyroid hormones**. A few cells called parafollicular cells or C cells lie between follicles. They produce the hormone **calcitonin** which helps regulate calcium balance.



Thyroid hormones:

Formation, Storage, and Release of Thyroid Hormones: Synthesis and secretion of T3 and T4 occurs as follows:

1 Iodide trapping: Thyroid follicular cells trap iodide ions (I-) from the blood into the cytosol. As a result, the thyroid gland normally contains most of the iodide in the body.

2 Synthesis of thyroglobulin: While the follicular cells are trapping I-, they are also synthesizing a glycoprotein thyroglobulin (TGB). The TGB is stored into vesicles which releases it into the lumen of the follicle.

3 Oxidation of iodide: The iodide ions trapped inside the follicular cell are converted into iodine molecules (I_2) by oxidation by peroxidase enzymes. As the iodide ions are being oxidized, they pass into the lumen of the follicle.

4 Iodination of tyrosine: As iodine molecules (I_2) form, they react with tyrosines (amino acids present in thyroglobulin molecules). Binding of one iodine atom yields monoiodotyrosine (T1) and binding of two iodine molecules produces diiodotyrosine (T2). The TGB with attached iodine atoms forms a sticky material called colloid which is stored lumen of the thyroid follicle.

5 Coupling of T1 and T2: During the last step in the synthesis of thyroid hormone, two T2 molecules join to form T4 or one T1 and one T2 join to form T3.

6 Pinocytosis and digestion of colloid: Droplets of colloid reenter follicular cells by pinocytosis and merge with lysosomes. Digestive enzymes in the lysosomes break down TGB and separates molecules of T3 and T4.

7 Secretion of thyroid hormones: Because T3 and T4 are lipid soluble, they diffuse through the plasma membrane into interstitial fluid and then into the blood.

8 Transport in the blood: More than 99% of both the T3 and the T4 combine with transport proteins in the blood, mainly thyroxine-binding globulin (TBG) for transportation.

Action of thyroid hormones:

a. Thyroid hormones increase basal metabolic rate (BMR), the rate of oxygen consumption under standard or basal conditions (awake, at rest and fasting) by stimulating the use of cellular oxygen to produce ATP. When the basal metabolic rate increases, cellular metabolism of carbohydrates, lipids, and proteins increases.

b. A second major effect of thyroid hormones is to stimulate synthesis of additional sodium-potassium pumps (Na+/K+ ATPase) which use large amounts of ATP for working. As cells produce and use more ATP, more heat is given off and body temperature rises. This phenomenon is called the calorigenic effect. Thus thyroid hormones play an important role in the maintenance of normal body temperature.

c. The thyroid hormones stimulate protein synthesis and increase the use of glucose and fatty acids for ATP production. They also increase lipolysis and enhance cholesterol excretion, thus reducing blood cholesterol level.

d. The thyroid hormones enhance some actions of the catecholamines (norepinephrine and epinephrine).

e. Together with human growth hormone and insulin, thyroid hormones accelerate body growth, particularly the growth of the nervous and skeletal systems. Deficiency of thyroid hormones during fetal development, infancy, or childhood causes cretinism which is characterized by severe mental retardation and stunted bone growth.

FUNCTIONAL DISORDERS

Two significant functional disorders characterised by distinct clinical syndromes are described. These are: *hyperthyroidism (thyrotoxicosis)* and *hypothyroidism.*

HYPERTHYROIDISM (THYROTOXICOSIS)

Hyperthyroidism, also called thyrotoxicosis, is a hypermetabolic clinical and biochemical state caused by excess production of thyroid hormones. The condition is more frequent in females and is associated with rise in both T3 and T4 levels in blood, though the increase in T3 is generally greater than that of T4.

ETIOPATHOGENESIS

Hyperthyroidism may be caused by many diseases but three most common causes are:
1, Graves' disease (diffuse toxic goitre),
2, toxic multinodular goitre and
3, a toxic adenoma.

Less frequent causes are hypersecretion of pituitary TSH by a pituitary tumour, hypersecretion of TRH, thyroiditis, metastatic tumours of the thyroid, Struma ovarii, congenital hyperthyroidism in the new-born of mother with Graves' disease, hCG-secreting tumours due to mild thyrotropic effects of hCG (e.g. hydatidiform mole, choriocarcinoma and testicular tumours), and lastly, by excessive doses of thyroid hormones or iodine called *Jod-Basedow disease.*

CLINICAL FEATURES

Patients with hyperthyroidism have a slow and insidious onset, varying in severity from case to case.

The usual symptoms are emotional instability, nervousness, palpitation, fatigue, weight loss in spite of good appetite, heat intolerance, perspiration, menstrual disturbances and fine tremors of the outstretched hands.
Cardiac manifestations in the form of tachycardia, palpitations and cardiomegaly are invariably present in hyperthyroidism.
The skin of these patients is warm, moist and flushed.

HYPOTHYROIDISM

Hypothyroidism is a hypometabolic clinical state resulting from inadequate production of thyroid hormones for prolonged periods, or rarely, from resistance the effects of thyroid hormones. The clinical manifestations of hypothyroidism, depending upon the age at onset of disorder, are divided into 2 forms:

1. *Cretinism* or *congenital hypothyroidism* is the development of severe hypothyroidism during infancy and childhood.
2. *Myxoedema* is the adulthood hypothyroidism.

Cretinism

A cretin is a child with severe hypothyroidism present at birth or developing within first two years of postnatal life. This is the period when brain development is taking place; in the absence of treatment the child is both physically and mentally retarded. The word *'Cretin'* is derived from the French, meaning *Christ like* because these children are so mentally retarded that they are incapable of committing sins. It can be induced because of variety of etiological rasons like: developmental anomalies, genetic defects, foetal exposure to iodide and antityroid drugs and *Endemic cretinism* in regions with endemic goitre due to dietary lack of iodine.

CLINICAL FEATURES

The clinical manifestations usually become evident within a few weeks to months of birth. The presenting features of a cretin are: slow to thrive, poor feeding, constipation, dry scaly skin, hoarse cry and bradycardia. As the child ages, clinical picture of fully-developed cretinism emerges characterised by impaired skeletal growth and consequent dwarfism, round face, narrow forehead, widelyset eyes, flat and broad nose, big protuberant tongue and protuberant abdomen.

Myxoedema

The adult-onset severe hypothyroidism causes myxoedema. The term myxoedema connotes non-pitting oedema due to accumulation of hydrophilic muco-polysaccharides in the ground substance of dermis and other tissues.

ETIOPATHOGENESIS:

1. Ablation of the thyroid by surgery or radiation.
2. Autoimmune (lymphocytic) thyroiditis (termed primary idiopathic myxoedema).
3. Endemic or sporadic goitre.
4. Hypothalamic-pituitary lesions.
5. Thyroid cancer.
6. Prolonged administration of antithyroid drugs.
7. Mild developmental anomalies and dyshormonogenesis.

CLINICAL FEATURES

The onset of myxoedema is slow and a fully-developed clinical syndrome may appear after several years of hypothyroidism. The striking features are cold intolerance, mental and physical lethargy, constipation, slowing of speech and intellectual function, puffiness of face, loss of hair and altered texture of the skin.

PANCREAS

Pancreas is both exocrine and endocrine gland. As an exocrine gland it secrets digestive juices called pancreatic juices. Pancreatic juice contains several enzymes which aid in digestion of food. As an endocrine gland, it secretes hormones like insulin, glucagon, somatostatin etc. Roughly 99% of the cells of the pancreas are arranged in clusters called acini. The acini produce digestive enzymes, which flow into the gastrointestinal tract through a network of ducts. Rest 1% of the cells are endocrine cells called **pancreatic islets** or **islets of Langerhans**. These cells produce hormones.

Each pancreatic islet includes four types of hormone-secreting cells:

1. Alpha or A cells: secrete **glucagon** which increases blood glucose level.

2. Beta or B cells: secrete **insulin** which decreases blood glucose level.

3. Delta or D cells: secrete **somatostatin** which inhibits both insulin and glucagon release. It also decreases absorption of nutrients from GIT.

4. F cells: secrete **pancreatic polypeptide** which inhibits somatostatin secretion, gall bladder contraction and secretion of digestive enzymes by pancreas.

DIABETES MELLITUS

As per the WHO, diabetes mellitus (DM) is defined as a heterogeneous metabolic disorder. DM is a leading cause of morbidity and mortality world over. It is expected to continue as a major health problem owing to its serious complications, especially end-stage renal disease, IHD, gangrene of the lower extremities, and blindness in the adults. Top 5 countries with highest prevalence of DM are India, China, US, Indonesia and Japan.

CLASSIFICATION AND ETIOLOGY

The older classification systems dividing DM into primary (idiopathic) and secondary types, juvenile-onset and maturity onset types, and insulin-dependent (IDDM) and non-insulin dependent (NIDDM) types.

TYPE 1 DM

It constitutes about 10% cases of DM. It was previously termed as juvenile-onset diabetes (JOD) due to its occurrence in younger age, and was called insulin-dependent DM (IDDM) because it was known that these patients have absolute requirement for insulin replacement as treatment.

Subtype 1A (immune-mediated) DM characterised by autoimmune destruction of β-cells which usually leads to insulin deficiency.

Subtype 1B (idiopathic) DM characterised by insulin deficiency with tendency to develop ketosis but these patients are negative for autoimmune markers.

Though type 1 DM occurs commonly in patients under 30 years of age, autoimmune destruction of β-cells can occur at any age. In fact, 5-10% patients who develop DM above 30 years of age are of type 1A DM and hence the term JOD has become obsolete.

TYPE 2 DM

This type comprises about 80% cases of DM. It was previously called maturity-onset diabetes, or non-insulin dependent diabetes mellitus (NIDDM) of obese and non-obese type.

PATHOGENESIS

Depending upon etiology of DM, hyperglycaemia may result from the following:

- Reduced insulin secretion
- Decreased glucose use by the body
- Increased glucose production.

NORMAL INSULIN METABOLISM *The major stimulus for both synthesis and release of insulin is glucose.* The steps involved in biosynthesis, release and actions of insulin are as follows:

Synthesis

Insulin is synthesised in the β-cells of pancreatic islets of Langerhans:

i) It is initially formed as *pre-proinsulin* which is single-chain 86-amino acid precursor polypeptide.

ii) Subsequent proteolysis removes the amino terminal signal peptide, forming *proinsulin*.

iii) Further cleavage of proinsulin gives rise to *A (21 amino acids) and B (30 amino acids) chains* of insulin, linked together by connecting segment called *C-peptide*, all of which are stored in the secretory granules in the β-cells. As compared to A and B chains of insulin, C-peptide is less susceptible to degradation in the liver and is therefore used as a marker to distinguish endogenously synthesised and exogenously administered insulin.

Release

Glucose is the key regulator of insulin secretion from β-cells by a series of steps:

i) Hyperglycaemia (glucose level more than 70 mg/dl or above 3.9 mmol/L) stimulates transport of glucose into β-cells by a *glu*cose *t*ransporter, *GLUT2*. Other stimuli influencing insulin release include nutrients in the meal, ketones, amino acids etc.

ii) An islet transcription factor, *glucokinase,* causes glucose phosphorylation, and thus acts as a step for controlled release of glucose-regulated insulin secretion.

iii) Metabolism of glucose to glucose-6-phosphate by glycolysis generates *ATP*.

iv) Generation of ATP *alters the ion channel activity* on the membrane. It causes inhibition of ATP-sensitive K+ channel on the cell membrane and opening up of calcium channel with resultant influx of calcium, which stimulates insulin release.

Action

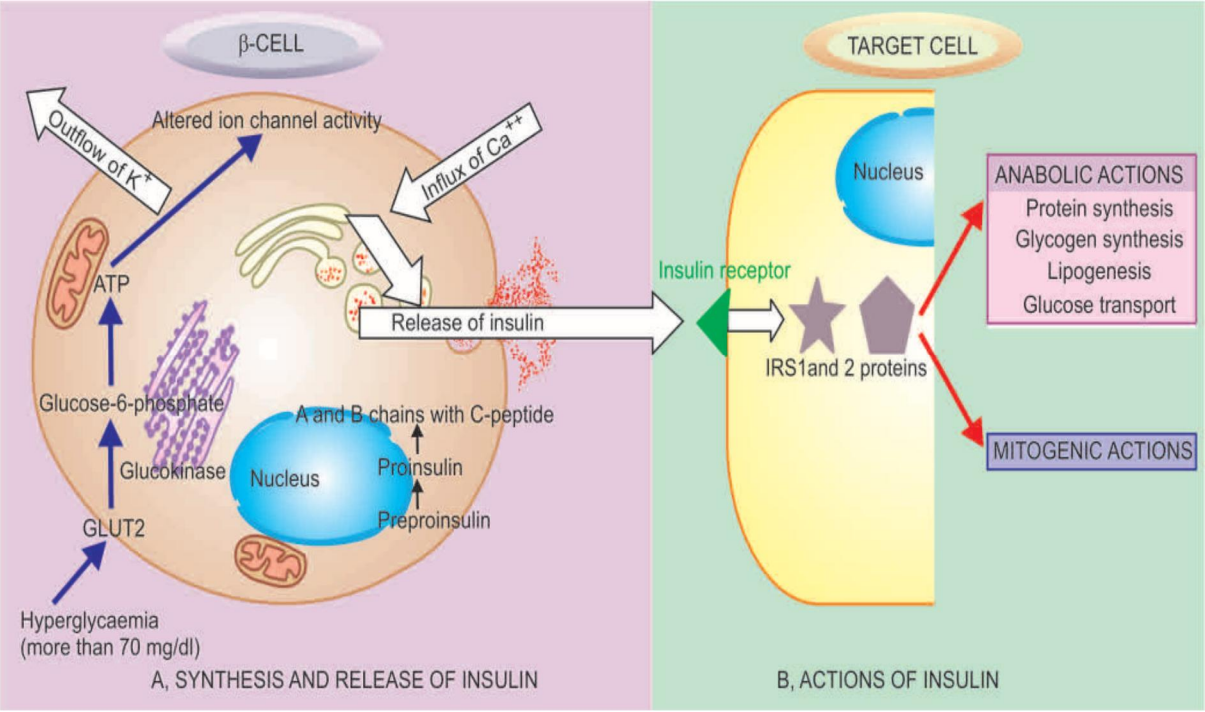
Half of insulin secreted from β-cells into portal vein is degraded in the liver while the remaining half enters the systemic circulation for action on the target cells:

i) Insulin from circulation binds to its receptor on the target cells. *Insulin receptor* has intrinsic tyrosine kinase activity.

ii) This, in turn, activates post-receptor intracellular signalling pathway molecules, *insulin receptor substrates (IRS) 1 and 2 proteins*, which initiate sequence of phosphorylation and dephosphorylation reactions.

iii) These reactions on the target cells are responsible for the main *mitogenic and anabolic actions of insulin*—glycogen synthesis, glucose transport, protein synthesis, lipogenesis.

iv) Besides the role of glucose in maintaining equilibrium of insulin release, *low insulin level in the fasting state* promotes hepatic gluconeogenesis and glycogenolysis, reduced glucose uptake by insulin-sensitive tissues and promotes mobilisation of stored precursors, so as to prevent hypoglycaemia.



PATHOGENESIS OF TYPE 1 DM

The basic phenomenon in type 1 DM is destruction of β*-cell mass, usually leading to absolute insulin deficiency.* While type 1B DM remains idiopathic, pathogenesis of type 1A DM is immune-mediated and has been extensively studied. Currently, pathogenesis of type 1A DM is explained on the basis of 3 mutually-interlinked mechanisms: genetic susceptibility, autoimmunity, and certain environmental factors.

1. Genetic susceptibility

Type 1A DM involves inheritance of multiple genes to confer susceptibility to the disorder:

i) It has been observed in *identical twins* that if one twin has type 1A DM, there is about 50% chance of the second twin developing it, but not all. This means that some additional modifying factors are involved in development of DM in these cases.

ii) About half the cases with genetic predisposition to type 1A DM have the *susceptibility gene* located in the HLA region of chromosome 6.

2. Autoimmunity

Studies on humans and animal models on type 1A DM have shown several immunologic abnormalities:

i) Presence of *islet cell antibodies* against GAD (glutamic acid decarboxylase), insulin etc, though their assay largely remains a research tool due to tedious method.

ii) Occurrence of lymphocytic infiltrate in and around the pancreatic islets termed *insulitis*.

iii) *Selective destruction of* β*-cells* while other islet cell types (glucagon-producing alpha cells, somatostatin-producing delta cells, or polypeptide-forming PP cells) remain unaffected. This is mediated by T-cell mediated cytotoxicity or by apoptosis.

iv) Role of *T cell-mediated autoimmunity* is further supported by transfer of type 1A DM from diseased animal by infusing T lymphocytes to a healthy animal.

v) Association of type 1A DM with *other autoimmune diseases* in about 10-20% cases such as Graves' disease, Addison's disease, Hashimoto's thyroiditis, pernicious anaemia.

vi) Remission of type 1A DM in response to immunosuppressive therapy such as administration of cyclosporine A.

3. Environmental factors

Epidemiologic studies in type 1A DM suggest the involvement of certain environmental factors in its pathogenesis, though role of none of them has been conclusively proved.

i) *Certain viral infections* preceding the onset of disease e.g. mumps, measles, coxsackie B virus, cytomegalovirus and infectious mononucleosis.

ii) *Experimental induction* of type 1A DM with certain chemicals has been possible e.g. alloxan, streptozotocin and pentamidine.

iii) *Geographic and seasonal variations* in its incidence suggest some common environmental factors.

iv) Possible relationship of early exposure to *bovine milk proteins* and occurrence of autoimmune process in type 1A DM is being studied.

PATHOGENESIS OF TYPE 2 DM

The basic metabolic defect in type 2 DM is either a delayed insulin secretion relative to glucose load *(impaired insulin secretion),* or the peripheral tissues are unable to respond to insulin *(insulin resistance).* Type 2 DM is a heterogeneous disorder with a more complex etiology and is far more common than type 1, but much less is known about its pathogenesis.

1. Genetic factors

Genetic component has a stronger basis for type 2 DM than type 1A DM. Although no definite and consistent genes have been identified, multifactorial inheritance is the most important factor in development of type 2 DM:

i) There is approximately 80% chance of developing diabetes in the other *identical twin* if one twin has the disease.

ii) A person with one parent having type 2 DM is at an increased risk of getting diabetes, but if *both parents* have type 2 DM the risk in the offspring rises to 40%.

2. Constitutional factors

Certain environmental factors such as obesity, hypertension, and level of physical activity play contributory role and modulate the phenotyping of the disease.

3. Insulin resistance

One of the most prominent metabolic features of type 2 DM is the lack of responsiveness of peripheral tissues to insulin, especially of the skeletal muscle and liver. Obesity, in particular, is strongly associated with insulin resistance and hence type 2 DM. Mechanism of hyperglycaemia in these cases is explained as under:

i) Resistance to action of insulin *impairs glucose utilisation* and hence hyperglycaemia.

ii) There is *increased hepatic synthesis* of glucose.

iii) *Hyperglycaemia in obesity* is related to high levels of free fatty acids and cytokines (e.g. TNF-α and adiponectin) affect peripheral tissue sensitivity to respond to insulin.

4. Impaired insulin secretion

In type 2 DM, insulin resistance and insulin secretion are interlinked:

i) Early in the course of disease, in response to insulin resistance there is compensatory increased secretion of insulin (*hyperinsulinaemia*) in an attempt to maintain normal blood glucose level.

ii) Eventually, however, there is *failure of* β-*cell function* to secrete adequate insulin, although there is some secretion of insulin i.e. cases of type 2 DM have mild to moderate deficiency of insulin (which is much less severe than that in type 1 DM) but not its total absence.

5. Increased hepatic glucose synthesis

One of the normal roles played by insulin is to promote hepatic storage of glucose as glycogen and suppress gluconeogenesis. In type 2 DM, as a part of insulin resistance by peripheral tissues, the liver also shows insulin resistance i.e. in spite of hyperinsulinaemia in the early stage of disease, gluconeogenesis in the liver is not suppressed. This results in increased hepatic synthesis of glucose which contributes to hyperglycaemia in these cases.