Iron Overload
= Haemochromatosis
= Haemosiderosis

Def:

Excess Fe in the body due to Fe entry or absorption over Fe loss which leads to tissue damage.

Haemochromatosis:

organ injury by systemic Fe overload,

Haemosiderosis:

single organ injury due to a defect in the organ itself.

Severe Fe overload:

defined as 5 gm excess & is specific for:

- Herediatry Haemochromatosis.
- Fe loading anaemia
- Sub-Saharan dietry Fe overload

Table 1: causes/ classifications:

Congenital	Acquired
• Hereditary Haemochromocytosis • Hereditary sideroblastic an. • Hereditary haemolytic an. - G6PD def., sickle cell an., Pyruvate kinase def., spherocytosis • Thalassamia major • Congenital dyserythropoietic an. • Congenital constitutional pure red cell aplasia • Porphyria cutanea tarda • Herediatry atransferrinemia • Herediatry aceruloplasinemia • Neonatal Haemochromocytosis	• Chronic ingestion of medical Fe. • Transfusion Fe overload • Acquired sideroblastic an. • African nutritional haemochromatosis • Siderosis associated e' splenorenal shunt

Table 2: The causes of iron overload

Increased iron absorption	Hereditary (primary) haemochromatosis Ineffective erythropoiesis, e.g. thalassaemia intermedia, sideroblastic anaemia Chronic liver disease
Increased iron intake	African siderosis (dietary and genetic)
Repeated red cell transfusions	Transfusional siderosis

Table 3: Causes of refractory anaemia that may lead to transfusional iron overload

Congenital	Acquired
β-Thalassaemia major	Myelodysplasia
β-Thalassaemia/Hb E disease	Red cell aplasia
Sickle cell anaemia ((some cases)	Aplastic anaemia
Red cell aplasia (Diamond–Blackfan)	Primary myelofibrosis
Sideroblastic anaemia	
Dyserythropoietic anaemia	

I- Genetic Haemochromatosis

A- Hereditary Haemochromatosis

Aeitology & pathogenesis:

-AR disorder characterized by:

-inborn error of Fe metabolism → slight ↑ in the rate of Fe absorption by GIT → accumulation of excess Fe along many years.

-manifest between 40-60ys.

-Excess Fe → accumulate in parenchymal cells

Tissue damage mainly in liver, pancreas, spleen & heart.

Aeitology & pathogenesis:

-Defect in regulation of Fe absorption at mucosal stage or at transfer stage.

-Mutation in HFE gene (gene that interacts e' the transferrin Receptors).

-Defect on short arm of chromosome no. 6.

-**2 types of mutations r found:**

G to A mutation at nucleotide 845 → Cystiene to Tyrosine substitution at amino acid 282 (C282T).

- C to G mutation at exon 2 → Histidine to Aspartic substitution at a.a. 63 (H63D).

Normally HFE membrane proteins →↓↓ Fe release from mucosal cells .

This defect in gene → defect in mucosal epith. of GIT →↑↑ rate of Fe transfer from mucosal cells to plasma.

Ferritin & Haemosidrin:

accumulate in most cells of the body:

- **liver:** hepatocytes & kupffer cs become loaded by ferritin & haemosedrin→ liver becomes:

-enlarged

-deep brown colour

-coarsely nodular

Heart: thickened myocardium & cardiomegaly.

Testes: atrophic.

Pancreas: diffuse fibrotic changes.

Histological studies proved:

Prominent hemosedrin depositionin many tissues & organs.

Effect of Fe on tissues→ tissue injury by:

Impairment of functions of MQ→↑ bacterial growth.

Generation of hydroxyl radicals→ cell damage.

Diagnosis:

Clinical picture:

- Homozygous → clinical manifestations in the 5th decade.

-Heterozygous→ No clinical expression

minor ↑ in serum Fe & ferritin

-Male: Female

5 : 1 due to Fe loss in menses & delivery.

- Weakness, lethargy, loss of weight, loss of libido.

-Arthritis: 2nd, 3rd meta carpo- phalengeal joints+ swelling & tenderness.

-Arthropathy: hip & knee.

-Skin hyper pigmentation (melanin deposition).

-Cardiac: arrhythmia, cardiomegaly, C.H.F.

- Hepatomegaly →hepatic cirrhosis, hepatoma

-Endocrinopathies:

DM due to pancreatic affection

hypothyrodism

testicular atrophy→ loss of libido, impotance

-Abdominal pain (may be due to hepatomegaly).

-Bacterial peritonitis

-May be splenomegaly.

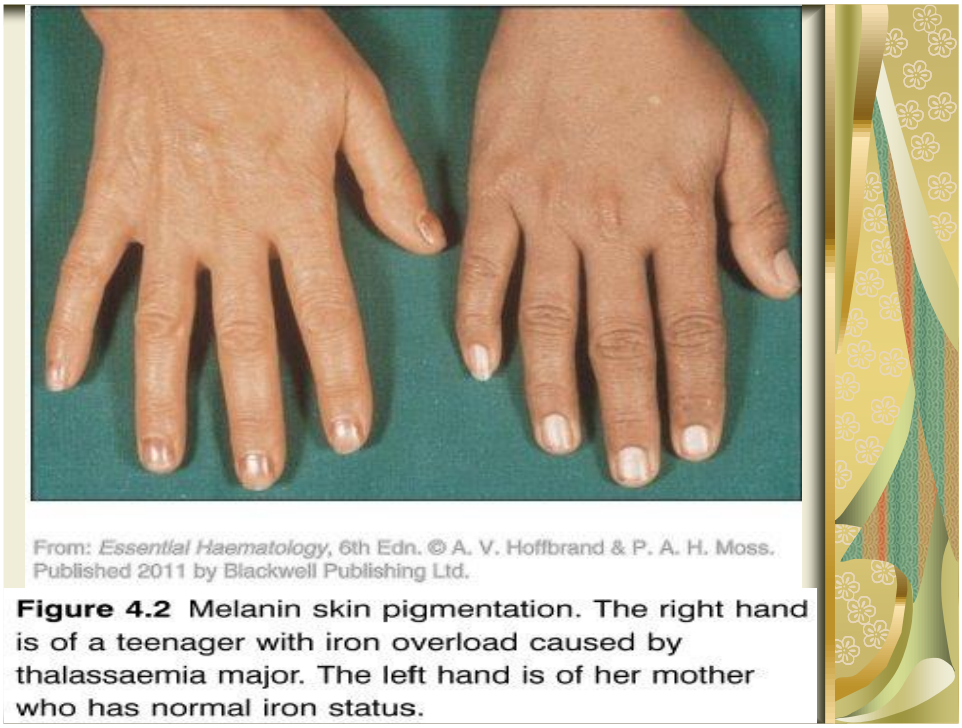

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Figure 4.2 Melanin skin pigmentation. The right hand is of a teenager with iron overload caused by thalassaemia major. The left hand is of her mother who has normal iron status.

Lab investigations:

CBC:

Normal except late in disease when splenomegaly occurs →↓Hb, ↓WBCs,↓ platelets.

Biochemical tests:

↑ serum Fe

↑ transferrin saturation> 60% may be up to >80%

↑ serum ferritin >1000 ug/L

Others:

Transferrin Index: $\frac{\text{serum Fe conc.}}{\text{serum transferrin conc.}}$ >1

Liver function tests: ↑ AST, ↑ALT.

Endocrinal Functions:

↓ thyroxine,↑ TSH

↓ pituitary gonadotropins,↓ androgens

Hyperglycemia, abnormal glucose tolerance test

Cardiac:

ECG, chest X-ray

Skin test:

I.D injection of 0.5 Ferrocyanide in 0.01 % HCL → +ve reaction → Blue colour appears e'in minutes.

Rous test:

Fe in urinary sediment.

Chelating method:

Desferroximine (urine Fe is measured after injecting 0.5 gm of des.)

Normal: 2 mg/24 hrs

Hemo. : 5mg/24 hrs

Liver biopsy: Fe overload

Hepatic Iron Index: diff hemochromatosis from alcoholic liver dis.

N: ↓ 2-8 mg/g liver

Hemo.: ↑ 5-6 mg/g liver

Alcohol.: ↓5-6 mg/g liver

Family study: HFE gene

Ferrokinetices: ↑ BM iron.

Diagnostic methods for Iron status:

3 compartments:

- storage Fe
- transport Fe
- functional Fe compounds (Hb)

± Ferrokinetices

I- Storage Iron:

A- serum Ferritin:

-correlates e' hepatic& MQ Fe stores

-ranges: M: 40-340 ug/L mean 100 ug/L

F: 15-150 ug/L mean 30 ug/L

-values ↓15 ug → Fe def. (but N values don't exclude).

-values ↑ 400 ug → Fe overload (in absence of other conditions).

as it is also ↑ in: inflammation (acute phase reactant).

malignancies (considered as tumor marker)

damage to tissues rich in ferritin.

Values ↑ 4000 ug : in transfusion dependent anaemia (e.g. thalasamia) indicates : liver dysfunction & Fe stores.

B- Tissue biopsy:

Liver : stained for Fe (Perussion Blue) → examine stores.

BM: also liver biopsy detects any liver damage.

C- Hepatic Iron Index:

Liver biopsy:

washed: to remove excess venous blood.

wrapped: in aluminum foil

dried: to constant weight

Then Fe estimated / weight

Values ↑ 15mg/gm liver → Fe overload

D- Hepatic Iron Index divided on age:

(as there is ↑ Fe deposition e' age)

Index > 2 Homozygous Haemochromatosis

Index 1-2 Heterozygous ,, or alcoholic

E- Chelating method:

Inject 0.5 gm desferroxamine then estimate urine Fe .

↑2 mg/ 24hrs ↑ Fe stores N: 2mg/24 hrs

F- Mobilization of Iron by Phlebotomy:

recurrent venesections r done → x Fe accumulation from absorption.

Amount of Fe in removed RBCs (before naemia develops) is measured. N: M: 750 mg F: 250mg

G- CT scan & MRI: for liver Fe (not sensitive as biopsy).

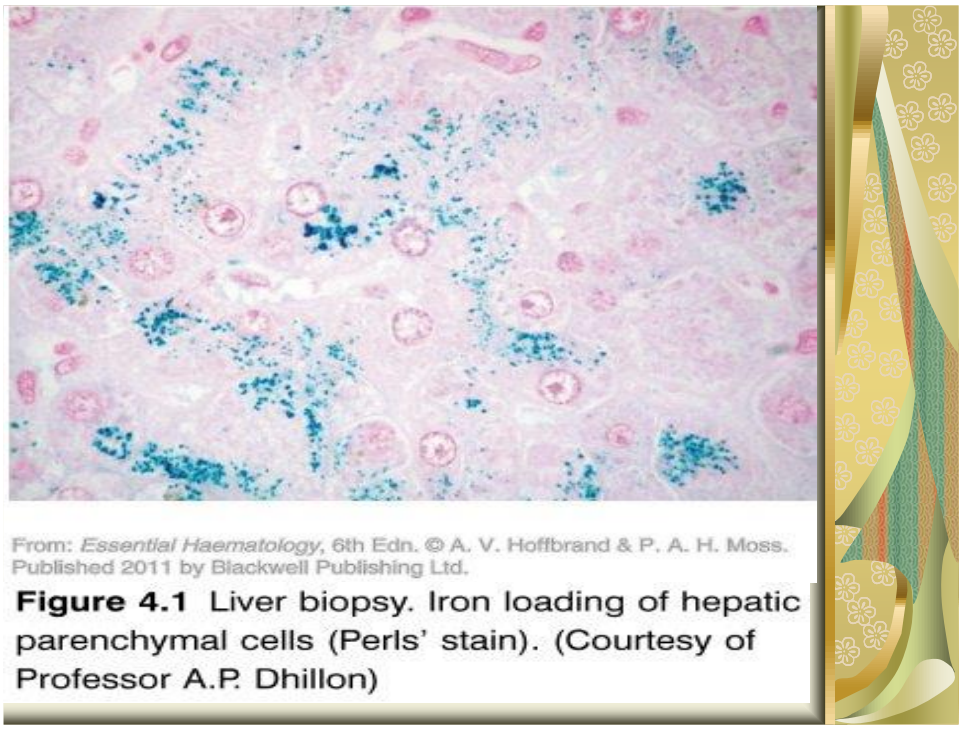
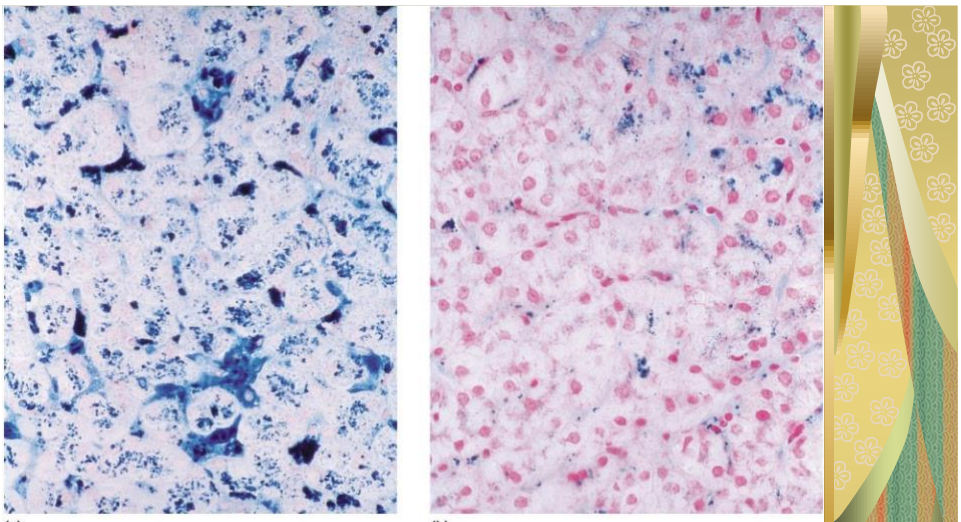
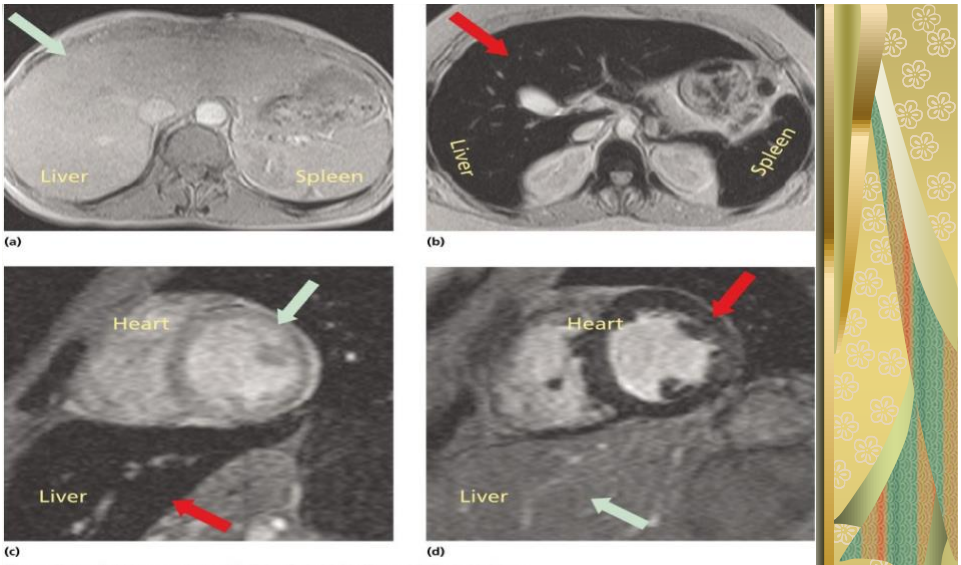


Figure 4.1 Liver biopsy. Iron loading of hepatic parenchymal cells (Perls' stain). (Courtesy of Professor A.P. Dhillon)



(a) (b)

Figure 4.3 β-Thalassaemia major: needle biopsy of liver. **(a)** Grade IV siderosis with iron deposition in the hepatic parenchymal cells, bile duct epithelium, macrophages and fibroblasts (Perls' stain). **(b)** Reduction of iron excess in liver after intensive chelation therapy.



(a) (b) (c) (d)

Figure 4.4 T2* magnetic resonance images (MRIs) showing tissue appearance in iron overload: **(a)** normal volunteer, **(b)** severe iron overload. Green arrow, normal appearance; red arrow, iron overload. Lack of correlation: liver and cardiac iron in two cases of thalassaemia major **(c)** and **(d)**. (Courtesy of Professor D.J. Pennell.)

II- Transport Iron:

A- Serum Iron:

N : 100-150 ug/dl

B- Transferrin saturation: (N: 30%)

↓ 15% e.g.: Fe def.

↑ 60% Fe overload

N.B: In children: lower values

In infections & chronic diseases: ↓ serum iron,

↓ transferrin sat (lactoferrin)

C- Serum Transferrin Receptors:

R $\frac{1}{\alpha}$ Fe supply

↑ on cells, serum in Fe def.

Serum N : 2.5-8.5 mg/L.

D- Red cell Ferritin:

It is better as a measure for parenchymal iron stores than serum ferritin.

↓ in Fe def. an.

↑ in disorders of Hb synthesis e.g: thalasamia.

E-Percentage of hypochromic cells:

values> 10% help to detect early impairment of Fe supply.

III- Haemoglobin concentration:

↓ Hb con // to Fe in Fe def. an.

but in megaloblastic an. , Hb ↓ but BM Fe ↑& serum ferritin ↑

IV- Ferrokinetics:

see later

<u>Treatment of hereditary haemochromatosis:</u>

Phlebotomy

Desferroxamine

Screening for relatives.

Table 4: Assessment of iron overload.

Assessment of iron stores
Serum ferritin
Serum iron and percentage saturation of transferrin (iron-binding capacity)
Serum non-transferrin bound iron
Bone marrow biopsy (Perls' stain) for reticuloendothelial stores
Liver biopsy (parenchymal and reticuloendothelial stores)
Liver CT scan or MRI
Cardiac MRI (T2* technique)
Deferoxamine or deferiprone urine iron excretion test (chelatable iron)
Repeated phlebotomy until iron deficiency occurs
Assessment of tissue damage caused by iron overload
Cardiac Clinical; chest X-ray; ECG; 24-hour monitor; echocardiography; radionuclide can to check left ventricular ejection fraction at rest and with stress
Liver Liver function tests; liver biopsy; CT scan or MRI
Endocrine Clinical examination (growth and sexual development); glucose tolerance test; pituitary
gonadotrophin release tests; thyroid, parathyroid, gonadal, adrenal function, growth
hormone assays; radiology for bone age; isotopic bone density study

B- Herediatry Aceruloplasminaemia

Aeitology:

AR

mutation of ceruloplasmin gene → x ceruloplasmin ferroxidase activity.

Pathogenesis:

-Fe accumulates in liver, pancreas, brain, & less extent in heart, kidney & spleen.

-Presents at middle age by DM, neurodegeneration of retina& basal ganglia.

Lab:

↓ serum iron

N TIBC

N or ↑ ferritin

ttt:

Desferroxamine ↓ brain iron

C-Hereditary Atransferrinaemia

AR rare

severe hypochromic an.

excess iron deposition in RES

Iron loading anaemia

1- Thalasamia major:

pathogenesis (causes of iron overload):

↑ iron absorption 2ry to disease

-E.V haemolysis

- I.V.H

- ineffective erythropoiesis

- repeated transfusion

- inhibition of haem synthesis by globin synthesis

-Defect in globin synthesis → ↓ globin synthesis → ↓ haem synthesis, iron enters the body → no usage of iron → Fe overload

2- Chronic Haemolytic Anaemia:

causes:

-E.V.H

-I.V.H

-ineffective erythropoiesis

-repeated transfision

3- Sideroblastic anaemia:

causes:

- ineffective erythropoiesis

-repeated transfision

II- Acquired Haemochromatosis

Sub-Saharan dietry iron overload:

African- nutritional haemochromatosis:

Excess iron ingestion from food or beer prepared in Fe pots (Bantu siderosis).

Localized Haemochromatosis: (Haemosiderosis):

Localized hge → Fe broken from RBCs is found by near by MQ.

Pulmonary haemosiderosis: minute hge in cases of mitral stenosis (MQ engulf Fe in lung) → Fe accumulate in lung (alveolar MQ).

Idiopathic haemochromatosis

Ferrokinetics

- Radioactive iron 59 Fe is injected IV → carried by transferrin to BM & stores in **60-140 min (Clearance time).**
- At this time radioactivity ↑over BM (site of erythropoiesis), then ↓through **10-14 days** (as newly formed RBCs pass to blood)
- **70-80%** of the dose appear in blood after **14 days (Red cell iron utilization),** it gives an idea about Effective erythropoiesis.
- The rest of the dose **25%** :

  15% : go to the stores

  10% : lost in ineffective erythropoiesis.

1- Plasma Iron Clearance (PIC):

59 Fe is mixed e' serum & injected in the patient IV.

It is carried by transferrin to BM & stores.

Time **60-140 min,** average **90 min**.

The time is shortened when:

↓ serum Fe

or erythroid activity ↑

At this time: radioactivity↑ over BM (site of erythropoiesis), then ↓through **10-14 days** (as newly formed RBCs pass to blood).

2- Red Cell Iron Utilization (RIU): 70-80%:

70-80% of the dose appears in blood after **14 days (RIU).**

It gives an idea about effective erythropoiesis.

It indicates the portion of marrow activity leading to production of viable RBCs.

It is calculated by finding the % of 59 Fe in circulating red cell mass **10-14 days** after injection.

3-Plasma Iron turnover (PIT):

It is a measure of total iron leaving plasma/ unit time.

It is calculated from iron clearance & plasma iron content .

It measures the iron taken by both erythroid & non erythroid tissues, (so must be corrected to find erythroid uptake).

It ↑↑ when erythroid marrow activity ↑↑.

PIT: gives an idea about total erythropoiesis (eff & ineff).

RIU: gives an idea about effective erythropoiesis.

4-Organ localization:

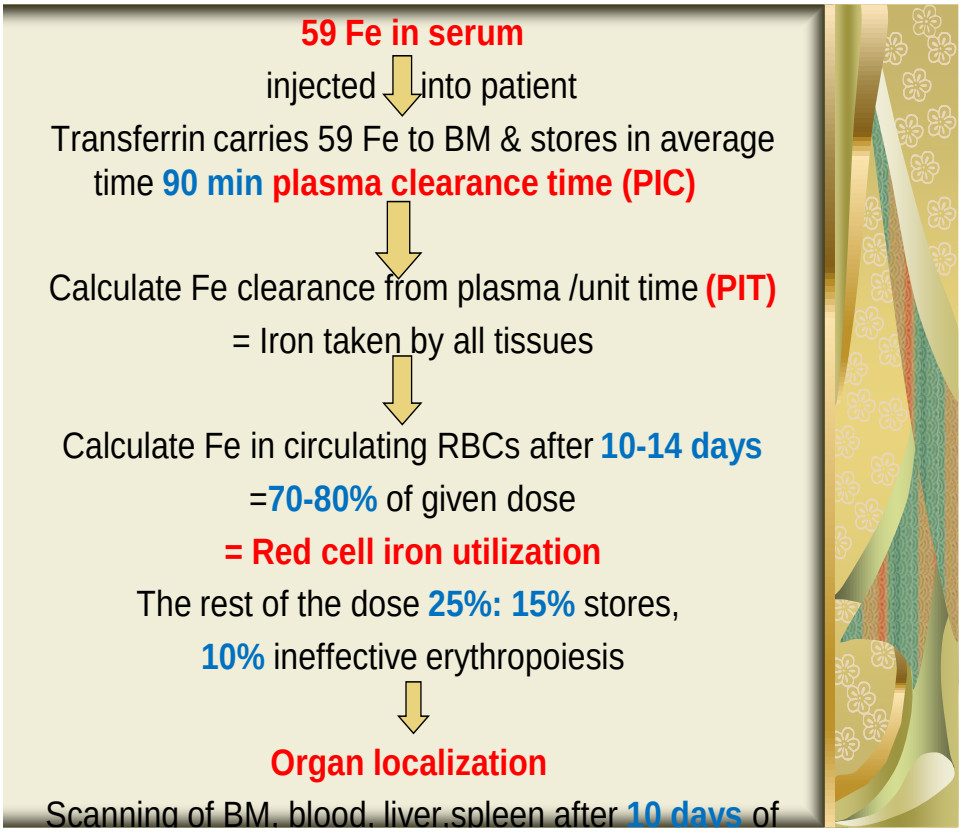
Organ scanning is used to find specific patterns of extramedullary haemopoiesis or haemolysis.

Scanning on :

BM blood

liver spleen

after **10 days** of injection.



Applications of ferrokinetics:

1- Normal pattern:

- When **59 Fe** is injected, it is carried by transferrin to BM & stores in **60-140 min** (Average 90 min) **PIC**.
- At this time, radioactivity of iron ↑ over the BM as it is the site of erythropoiesis
- Then, radioactivity of iron ↓ gradually over the BM in a peroid of **10-14 days** as newly formed RBCs r released into circulation.
- **70-80%** of radioactive dose appear in circulation after **14 days.**
- The rest of the dose **20-30%** go to the stores (liver, spleen) & some of it is lost as ineffective erythropoiesis.

2- Aplastic anaemia: بطئ

- Slow plasma clearance.
- Little uptake of Fe by BM.
- Accumulation of Fe in liver, spleen e' progressive enlargement.
- ↓ entry of radioactivity in circulation after 14 days.
- ↓ red cell Fe utilization (↓70-80%).

3- Haemolytic anaemia: السريع

- Rapid plasma clearance (↓ 60 min).
- Rapid ↑ of radioactivity on BM.
- Rapid appearance in blood (cir).
- ↑ radioactivity over liver, spleen due to haemolysis & extramedullary haematopoiesis.

4- Extramedullary Haematopoiesis: (erythropoiesis):

- -Little uptake of Fe by BM.
- -Initial accumulation of radioactivity in the organ, then it↓ e' the appearance of RBCs in circulation.
- -Rapid plasma clearance.

5- Ineffective Erythropoiesis:

- -Rapid clearance.
- ↑ activity over BM.-
- ↓ entry of radioactivity in circulation after 14 days
- (↓RIU).