Diyala University – collage of medicine
Hematology -5th stage

IRON DEFICIENCY ANEMIA

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Anemia

- **Definition :** decrease in Hb concentration below normal range to age and sex, either with decrease in RC count (absolute) or with normal RC count (relative).
- There are **three primary causes** of anemia:
  1. **reduced production of RBCs**
  2. **excessive destruction of RBCs**
  3. **excessive blood loss**

Classification

Etiological classification

A. **Anemias due to impaired red cell production**

- Nutritional deficiencies
  - Deficiencies affecting hemoglobin synthesis: Iron deficiency
  - Deficiencies affecting DNA synthesis: Vitamin B_{12} and folic acid deficiencies
  - Vitamin C deficiency
- Immune-mediated injury to progenitors
  - Aplastic anemia
  - Pure red cell aplasia
- Primary hematopoietic neoplasms
  - Acute leukemia
  - Myelodysplastic syndromes
  - Myeloproliferative neoplasms
- Miscellaneous
  - Anemia of chronic disorders
  - Marrow suppression due to drugs

Classification

- **Etiological classification**

1. ↓ production of RBC
   A. Nutritionals
   B. Immune destruction of progenitor
   C. Haemopoietic neoplasm
   D. Miscellaneous
2. ↑ Destruction of RBC(intravascular and extravascular hemolysis

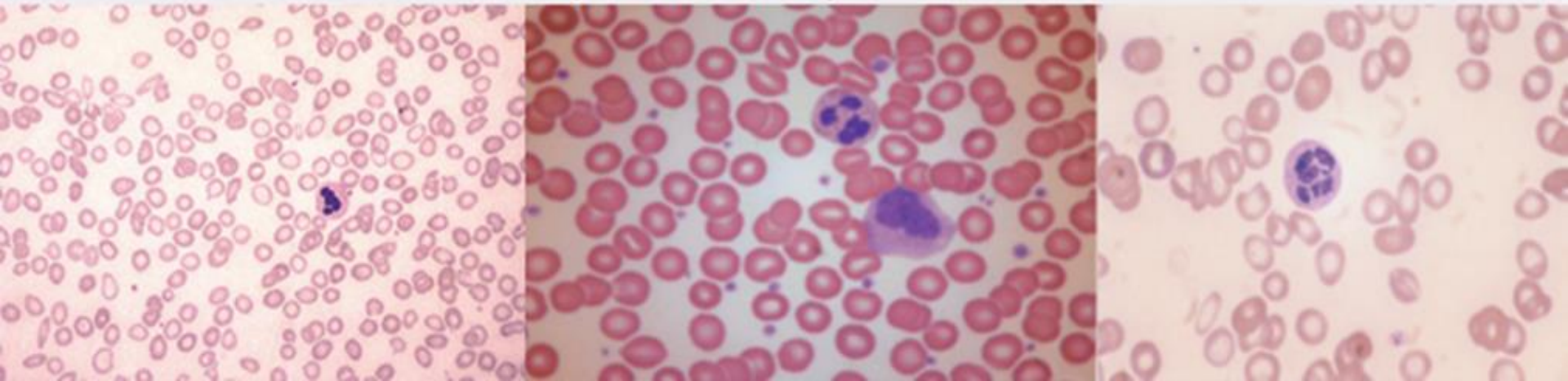
   - **Intravascular**
     - **Inherited(HEM)** → **H** (Hbpathies)
       - **E** (Enzymopathies)
       - **M** (Memberneopathies)
     - **Acquired** → **PNH**

- **Extravascular hemolysis** → immunohemolytic anemia
  - fragmentation syndrome
  - hypersplinsm

3.Anemia due to blood loss → acute (trauma)
- chronic(GIT or GUT bleeding

Morphological classification

Microcytic, hypochromic	Normocytic, normochromic	Macrocytic
MCV <80 fL MCH <27 pg	MCV 80–95 fL MCH ≥27 pg	MCV >95 fL
Iron deficiency Thalassaemia Anaemia of chronic disease (some cases) Lead poisoning Sideroblastic anaemia (some cases)	Many haemolytic anaemias Anaemia of chronic disease (some cases) After acute blood loss Renal disease Mixed deficiencies Bone marrow failure (e.g. post-chemotherapy, infiltration by carcinoma, etc.)	Megaloblastic: vitamin B_{12} or folate deficiency Non-megaloblastic: alcohol, liver disease, myelodysplasia, aplastic anaemia, etc. (see Table 5.10)



Blood film role in anemias

- Assessment size of RBC
- Assessment morphology of RBC
- Assessment morphology of WBC
- Assessment of platelets
- Diagnosis of parasitic infestation – as in malaria.

Iron Deficiency anemia:

Iron metabolism

- Iron present in tow forms (Ferrous F+2, Ferric F+3).
- Distribution of body iron:
  - ✓ **Total body iron 3-5 gm.** Store iron 10-12 mg/kg in M or 3-4 mg/kg in F.
  - ✓ **70% of body iron is physiological and 30% stored.**
  - ✓ **Storage** is present in forms of Ferritin and hemosidrin, in reticuloendothelial system (in bone marrow, spleen and liver), and paranchymal liver cells (gaining their Iron from plasma transferrin) (~20-25%(

Iron absorption:

- Normal mixed diet contains about **10-20 mg** of iron /day.
- Dietary sources include: meats especially liver and kidney, egg yolk, some green vegetables like Peas, lentil and beans. Milk has low iron content generally.
- **Usually only 5-10% of ingested iron is absorbed**.
- After ingestion of iron containing foods, maximally absorbed in duodenum and less so Jejunum.

Iron regulatory protein

- **Transferrin**
- **DMT1 (Divalent metal transporter 1).** is an iron transport protein from the GI lumen into the duodenal enterocytes (uptake)
- **Ferroportin 1**: is an iron transport protein at the duodenal enterocyte basolateral membrane; macrophage cytoplasm; hepatocyte sinusoidal membrane.(release)
- **Hepcidin** It is both an acute phase protein and the major hormonal regulator of iron homeostasis, - Hepcidin synthesis and secretion are controlled by three proteins: HFE, hemojuvelin and transferrin receptor 2

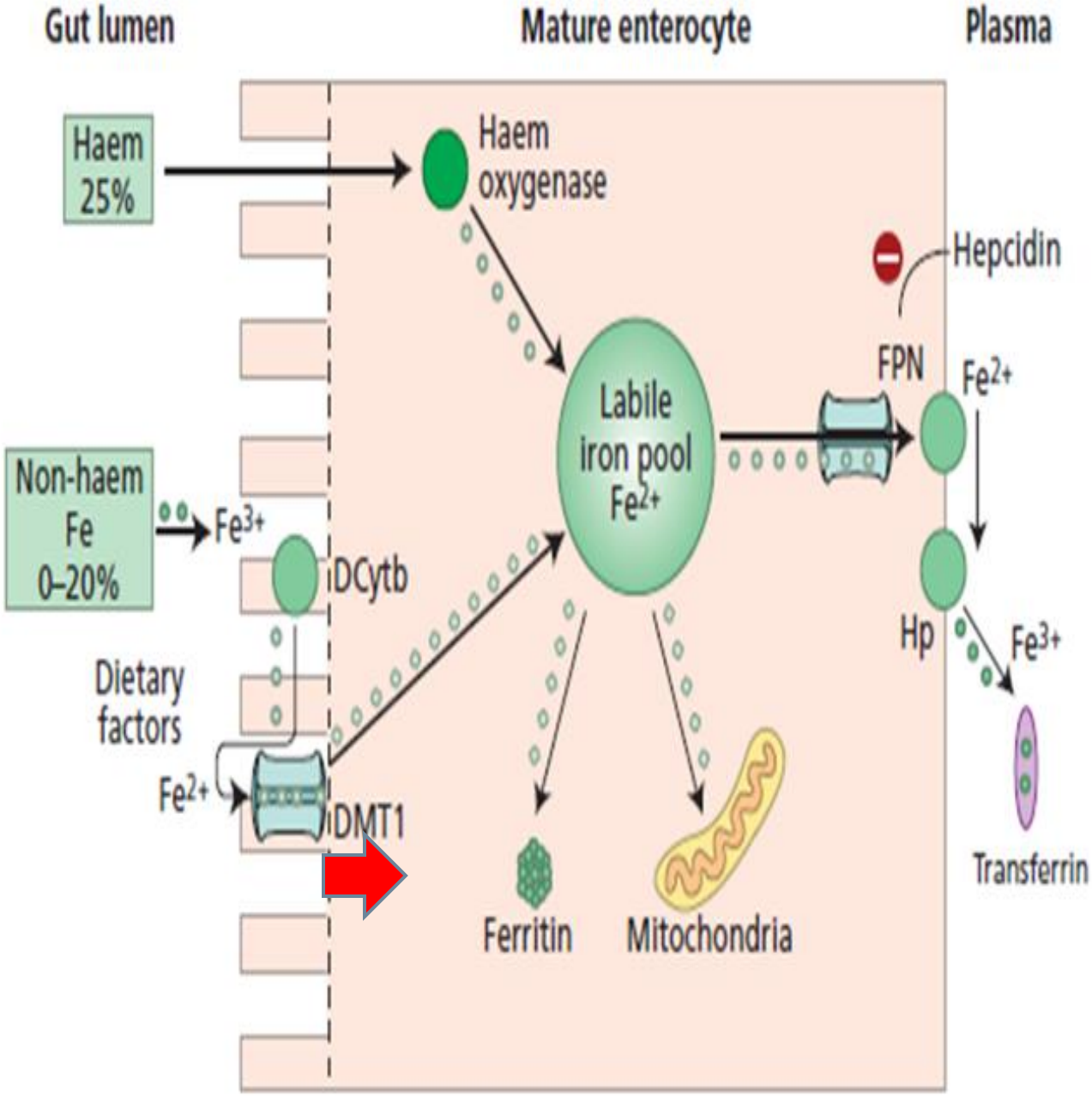


Figure 3.4 Molecular pathways of iron absorption. The area enclosed in the dotted box refers to the uptake of iron from the plasma in the developing enterocyte in the intestinal crypt. Otherwise, the diagram refers to iron absorption by the villous epithelial cell. DMT1, divalent metal transporter 1; FPN, ferroportin. Hp, hephaestin. For further details see text and Table 3.1.

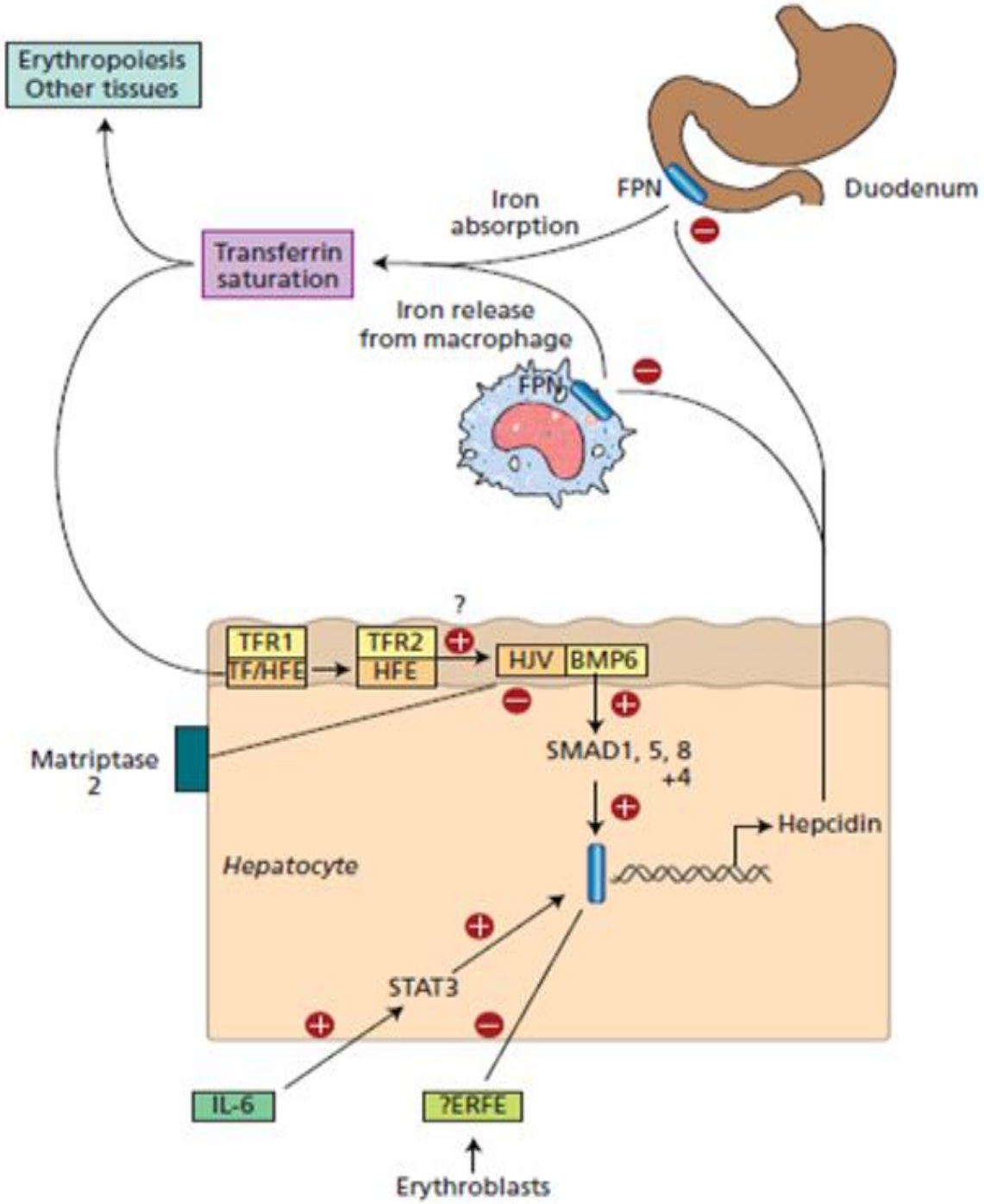


Figure 3.2 Stimulatory and inhibitory signals of hepcidin regulation. Hepcidin, as well as hemojuvelin (HJV), transferrin receptor 2 (TFR2) and HFE, are all produced in the hepatocyte. High plasma iron and inflammation stimulate hepcidin synthesis. This is mediated by SMADs and STAT3, respectively. Conversely, low plasma iron, increased rates of erythropoiesis (including ineffective erythropoiesis) and hypoxia inhibit hepcidin production. This is mediated by matriptase and ERFE. Hepcidin binds ferroportin (FPN), causing its destruction and so inhibits iron absorption and iron release from macrophages into plasma and from intracellular compartments. BMP, bone morphogenetic protein; ERFE, erythroferrone; The ? indicates uncertainty of the ERFE function in humans; GDF-15 may be the human equivalent of ERFE.

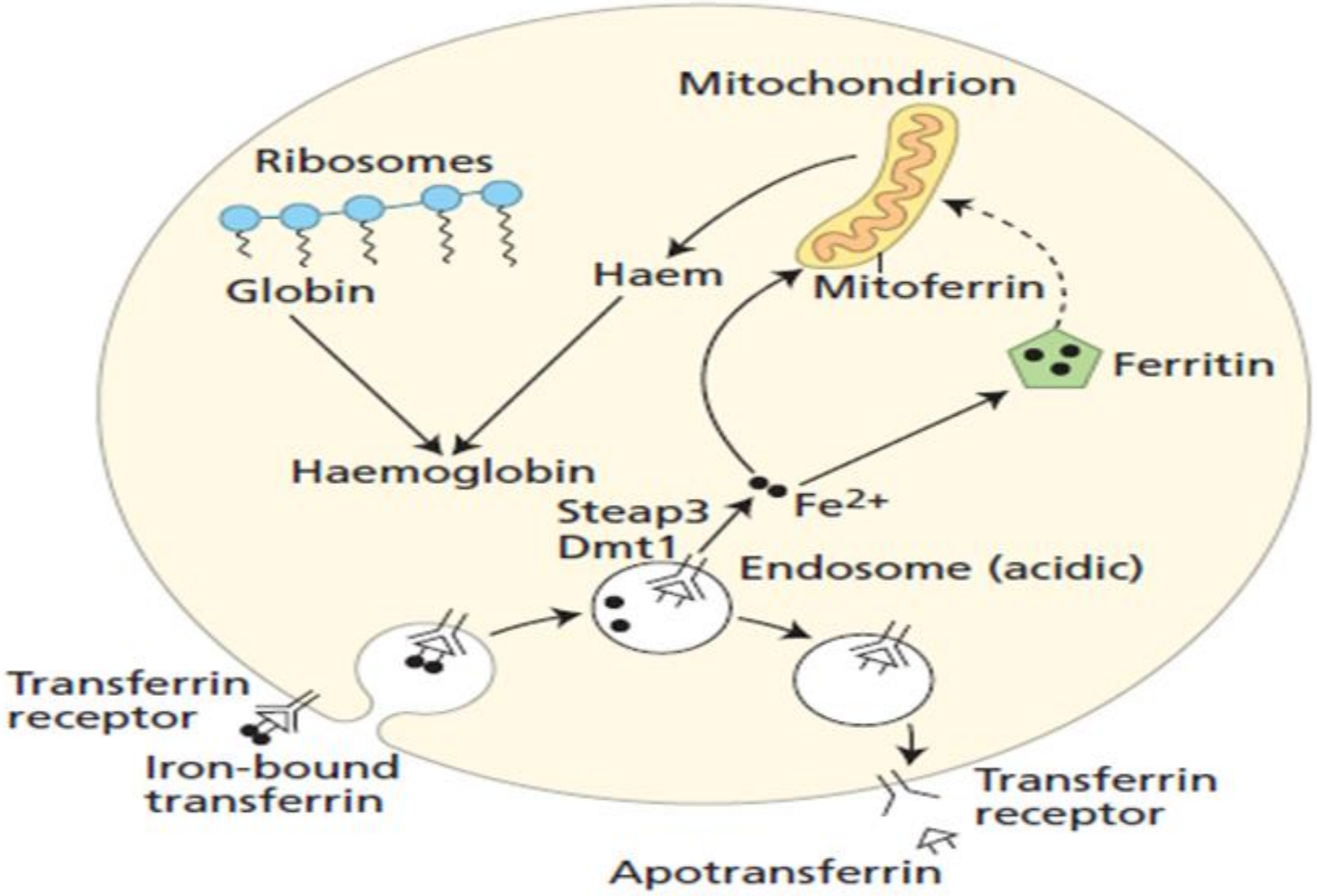


Figure 3.5 Incorporation of iron from plasma transferrin into haemoglobin in developing red cells. Uptake of transferrin iron is by receptor-mediated endocytosis.

Iron absorption regulation

- The body iron stores are reflected in the cytoplasmic iron content of mucosal intestinal cells. And if :
  - ✓ Body stores are high, so is mucosal cell iron : iron absorption from intestinal lumen is prevented, and mucosal cells with their iron are shed into lumen (physiological(
  - ✓ Body stores are low, so is mucosal cell iron: the mucosal cells permit absorption
- **Total losses** of Iron/day ~ 1 mg is counter balanced by a daily absorption of ~ 1 mg from diet and occur through:
  - ✓ Shedding of intestinal cells and macrophages in stool.
  - ✓ Urine.
  - ✓ Nails, hair and desquamated skin cells.
  - ✓ Menstruation in females.

Factors favoring absorption

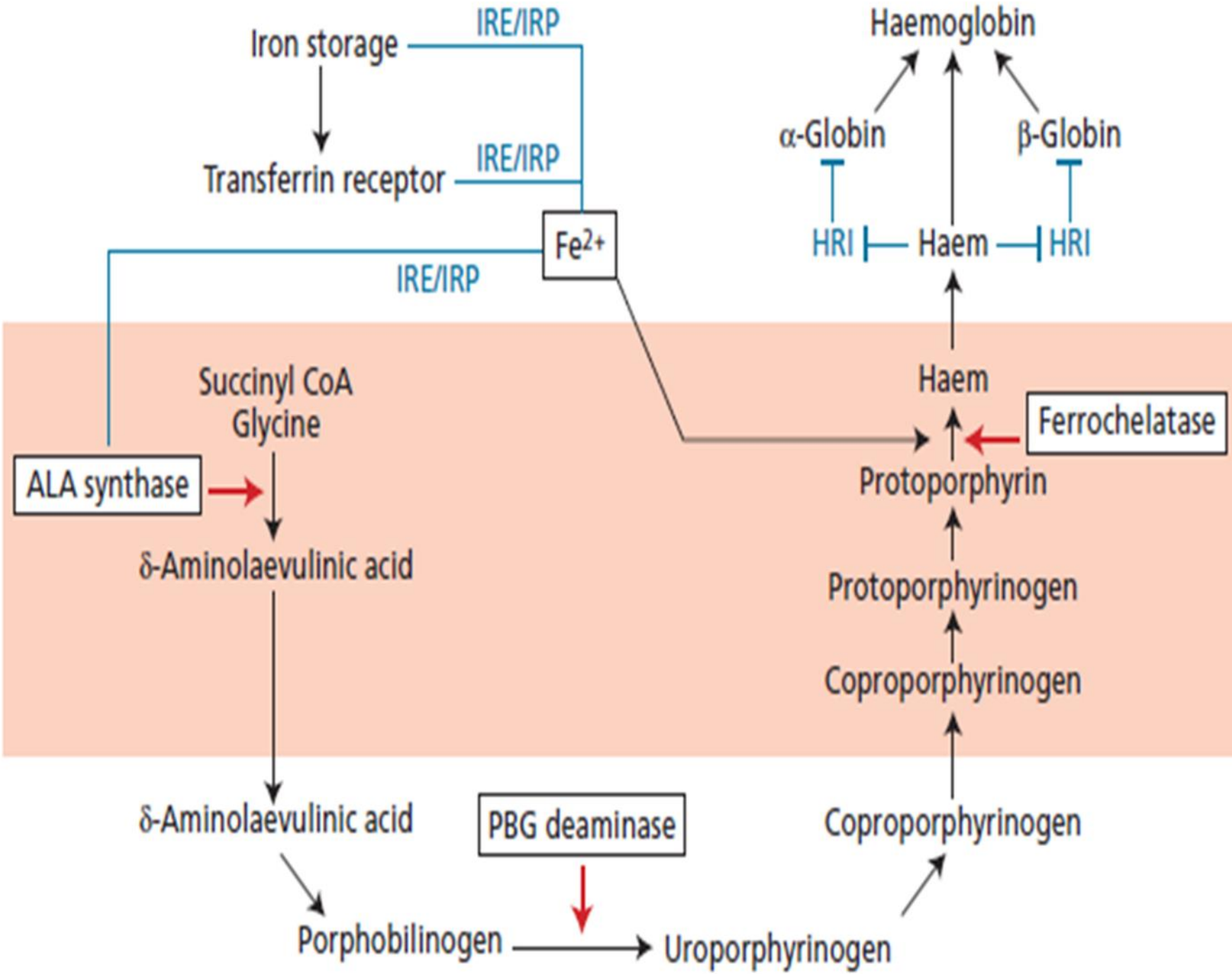
- Increase haem iron
- Increase animal food
- Fe+2
- Acidic PH (gastric)
- Solubilized agents (vitamin C, sugar, AA)
- IDA, Pregnancy.
- Hereditary hemochromatosis
- Increase expression of DMT-1 and ferroportin.

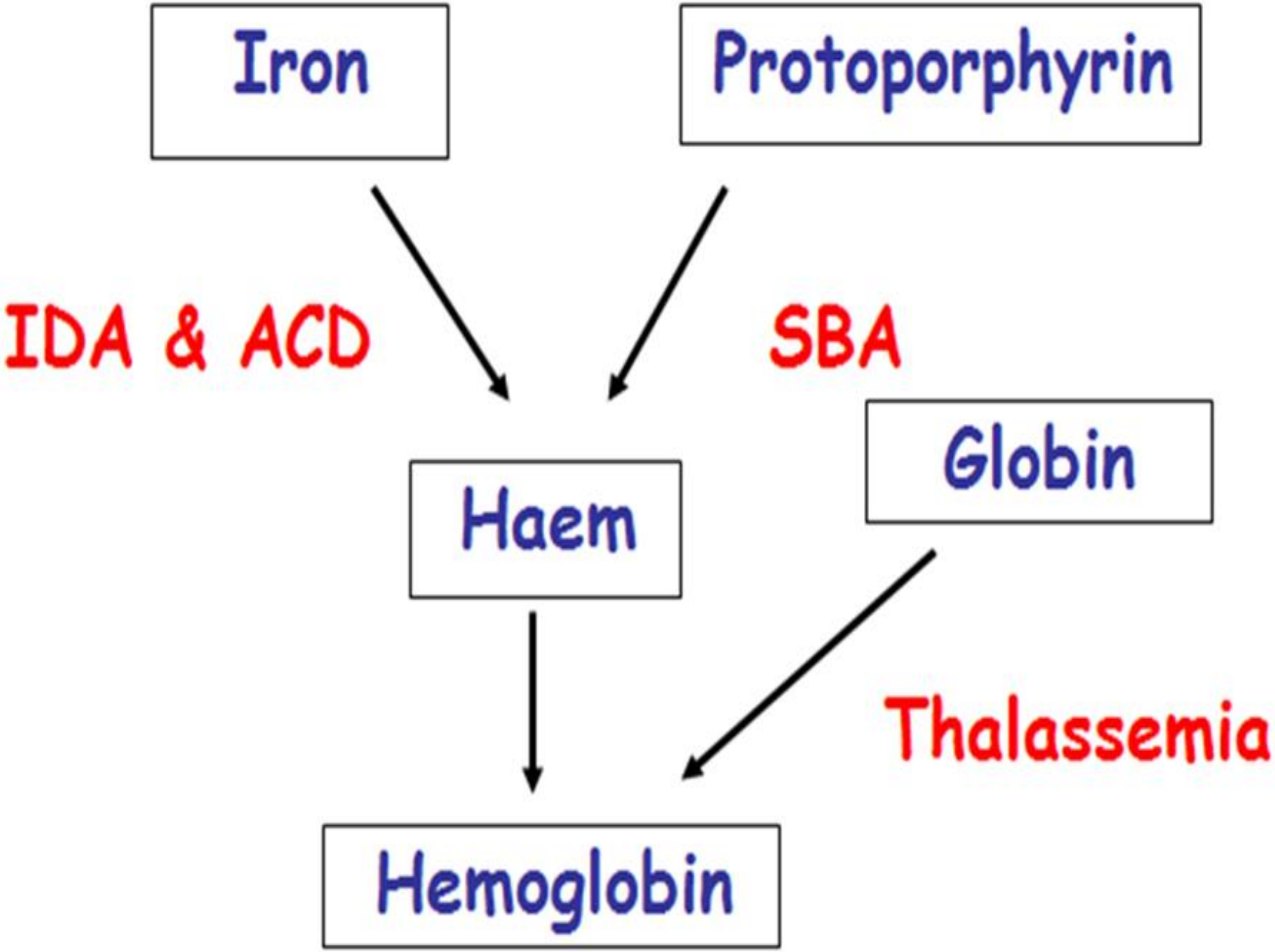
Factors reduce absorption

- decrease haem iron
- decrease animal food
- Fe+3
- Alkaline PH (pancreatic)
- precipitating agents (phytate, tannate in tea, phosphates)
- Iron overload.
- decrease expression of DMT-1 and ferroportin.

Pathogenesis of Iron Deficiency Anemia

- Iron Deficiency Anemia is the **most common form** of anemia,
- It is more common in **developing countries** like ours.
- **Three pathogenic factors** are implicated in the anemia of iron deficiency.
  - ✓ **Hemoglobin synthesis** is impaired as a consequence of reduced iron supply.
  - ✓ There is a generalized defect in **cellular proliferation.**
  - ✓ **Survival of erythroid precursors** and erythrocytes is reduced, particularly when the anemia is severe.


Iron storage
IRE/IRP
Transferrin receptor
IRE/IRP
Fe2+
IRE/IRP
Haemoglobin
α-Globin
β-Globin
HRI
Haem
HRI
Succinyl CoA
Glycine
ALA synthase
δ-Aminolaevulinic acid
Haem
Ferrochelatase
Protoporphyrin
Protoporphyrinogen
Coproporphyrinogen
δ-Aminolaevulinic acid
PBG deaminase
Coproporphyrinogen
Porphobilinogen
Uroporphyrinogen


Iron
Protoporphyrin
IDA & ACD
SBA
Globin
Haem
Thalassemia
Hemoglobin

Sequence of events to develop IDA

1. **Depletion of iron stores**
2. **Iron-deficient erythropoiesis**
3. **Iron deficiency anemia**

Causes of Iron Deficiency:

1. **Chronic Blood Loss :** (6-8 ml/day) Most likely from the gastrointestinal tract (hookworm infestation common cause, duodenal ulcer,).
2. **Increase in demand** :Prematurity and Infancy (3-6 months), pregnancy, lactation, menstruation and adolescence period.
3. **Nutritional:** Rarely to be the sole cause of ID but quite common cause of Iron deficiency in developing and underdeveloped countries, especially if inadequate intake is coupled with increased demand.
4. **Inadequate absorption:** Malabsorption syndromes e.g. celiac disease.

Laboratory Diagnosis of IDA :

1. **Hematological findings:**
   - ✓ Reduce in Hb (6-8gm/dl).
   - ✓ Reduce PCV, MCV, MCH, and MCHC.
   - ✓ Retic count is low to degree of anemia.
   - ✓ WBC usually normal, and Platelets counts often increase.
   - ✓ **Blood film:** Hypochromic Microcytic, with occasional rod and target cells.
   - ✓ **BM:** Micronormoblastic maturation, with decrease or absence in marrow iron store (Perl's stain/ Prussian blue stain) which is diagnostic

	Parameter				
1	WBC		7.80	10^9/L	4.00 -
2	Neu#		4.34	10^9/L	2.00 -
3	Lym#		3.08	10^9/L	0.80 -
4	Mon#		0.32	10^9/L	0.12 -
5	Eos#	L	0.01	10^9/L	0.02 -
6	Bas#		0.05	10^9/L	0.00 -
7	Neu%		55.6	%	50.0 -
8	Lym%		39.5	%	20.0 -
9	Mon%		4.1	%	3.0 -
10	Eos%	L	0.1	%	0.5 -
11	Bas%		0.7	%	0.0 -
12	RBC	L	3.24	10^12/L	3.50 -
13	HGB	L	5.4	g/dL	11.0 -
14	HCT	L	19.3	%	37.0 -
15	MCV	L	59.7	fL	80.0 -
16	MCH	L	16.7	pg	27.0 -
17	MCHC	L	28.0	g/dL	32.0 -
18	RDW-CV	H	23.5	%	11.0 -
19	RDW-SD		53.3	fL	35.0 -
20	PLT		253	10^9/L	100 -
21	MPV		7.8	fL	6.5 -
22	PDW		15.2		9.0 -
23	PCT		1.98	mL/L	1.08 -

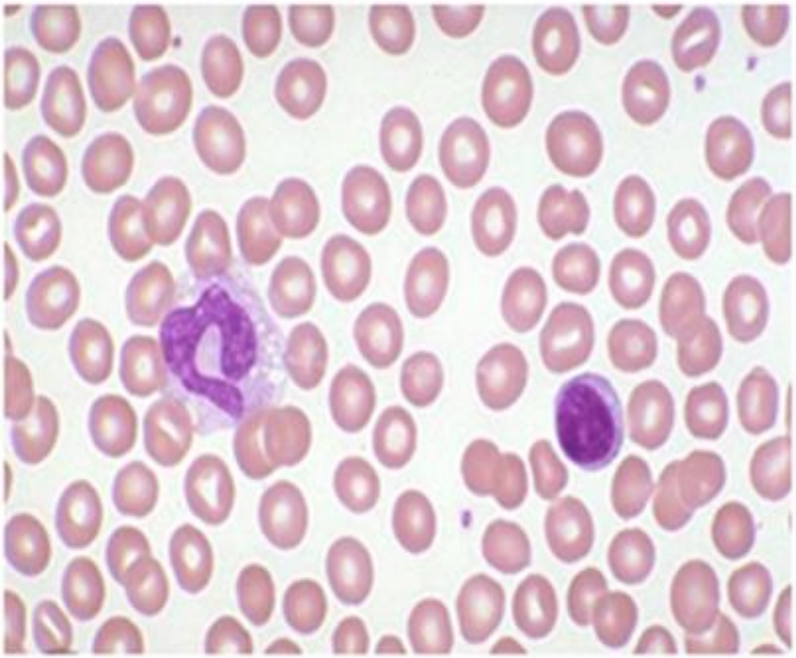
cian:
v Time:
mments:

Operator:
Delivery time:

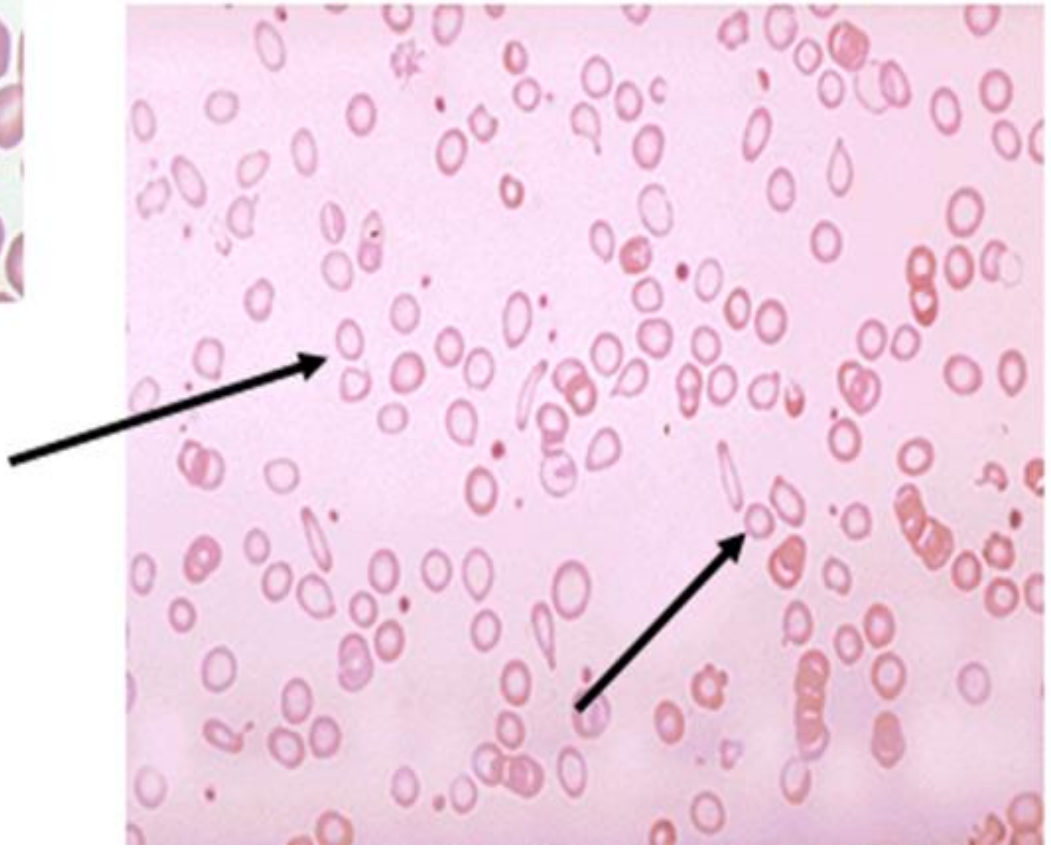
Administrator

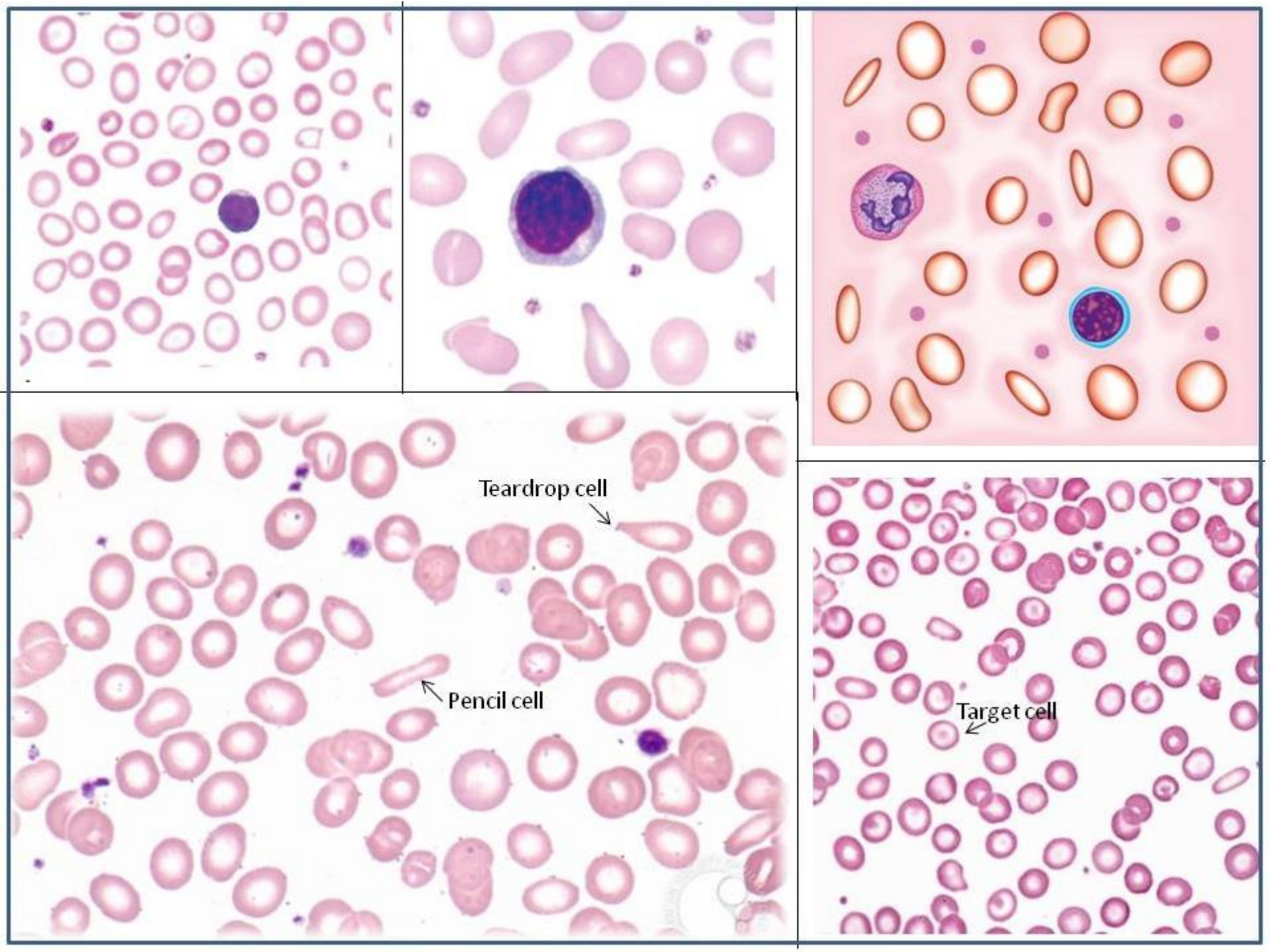
report only applies to the corresponding sample analyzed]

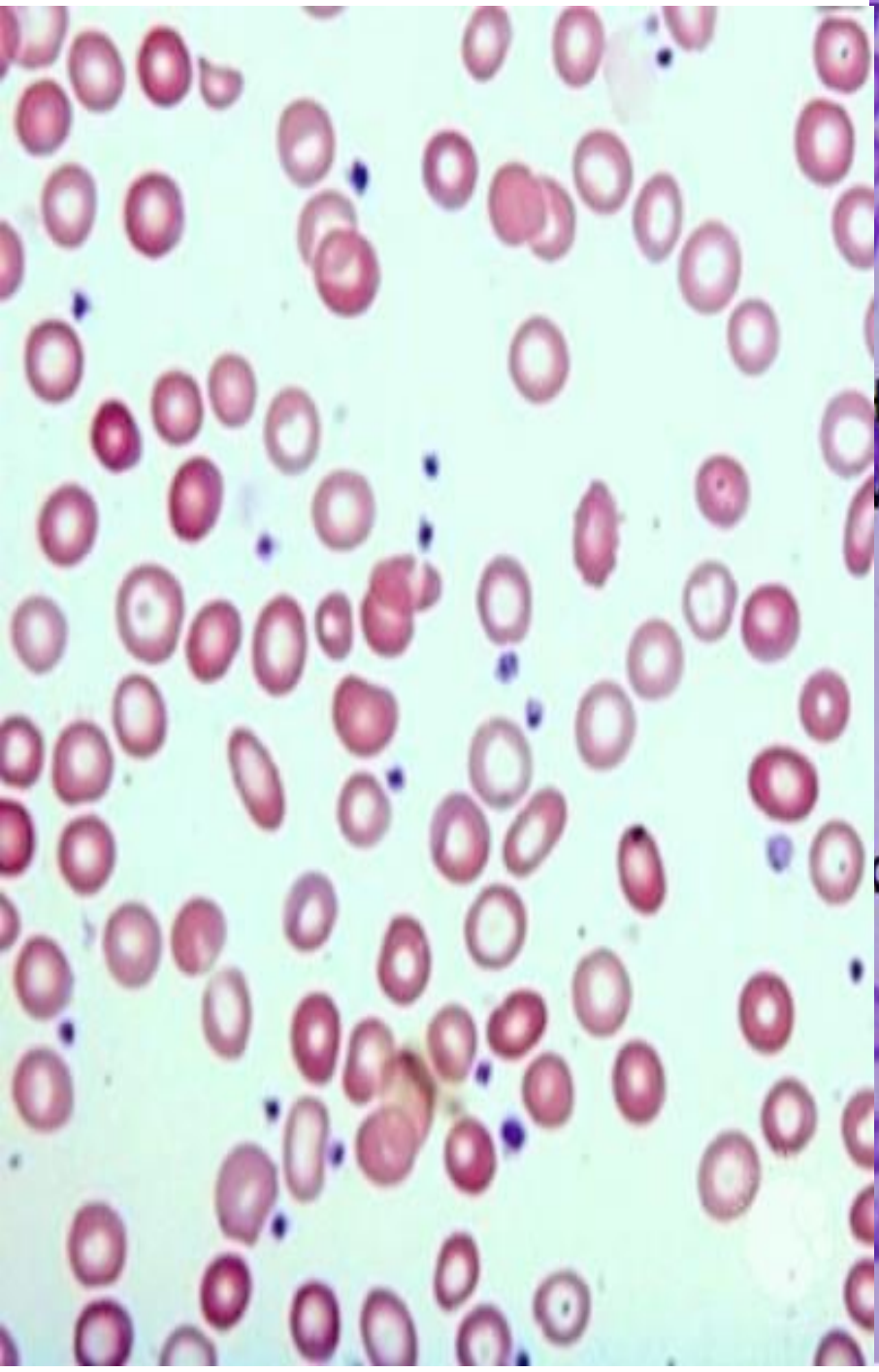
Normochromic Normocytic

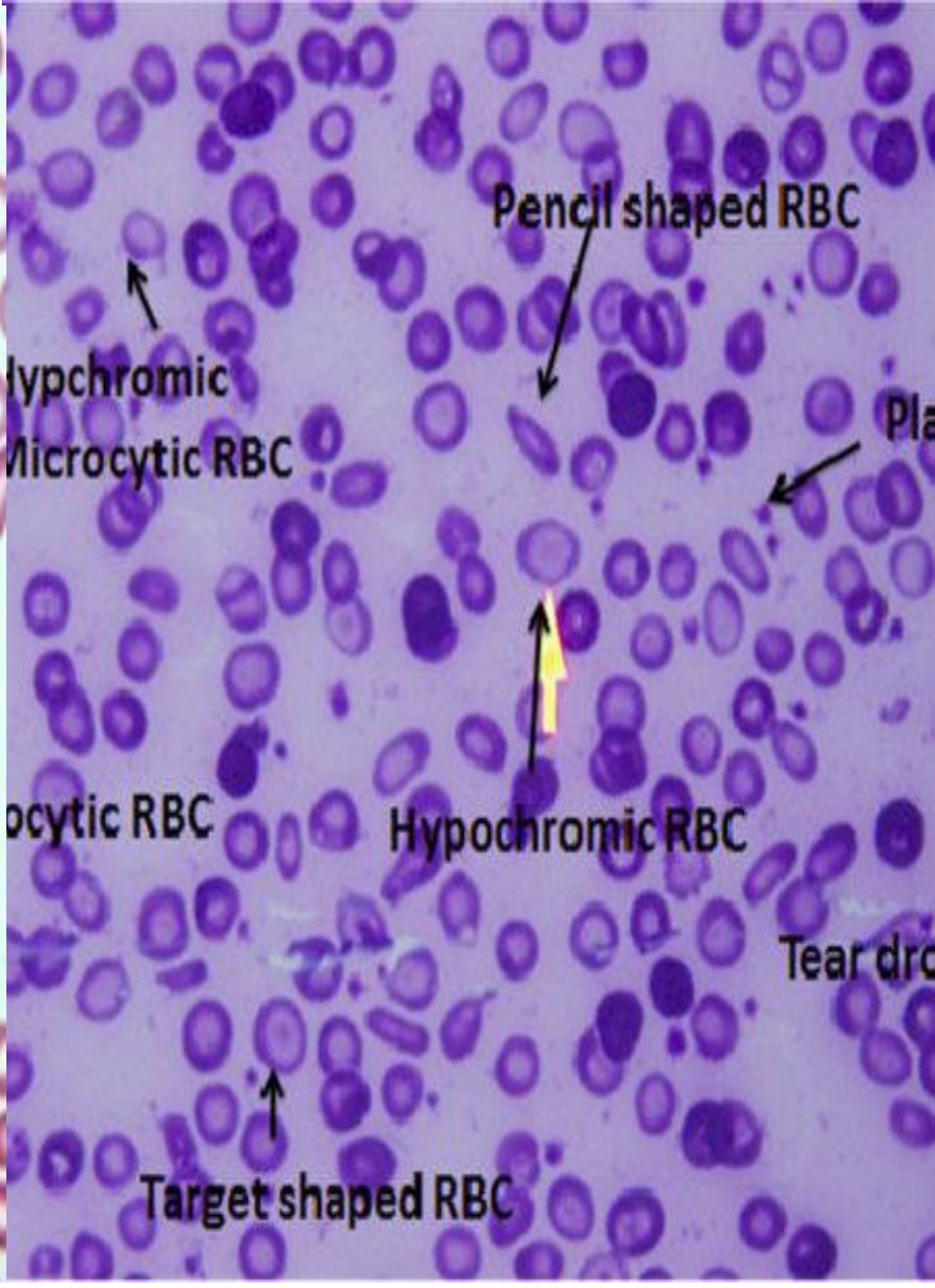


Hypochromic microcytic




Teardrop cell
Pencil cell
Target cell

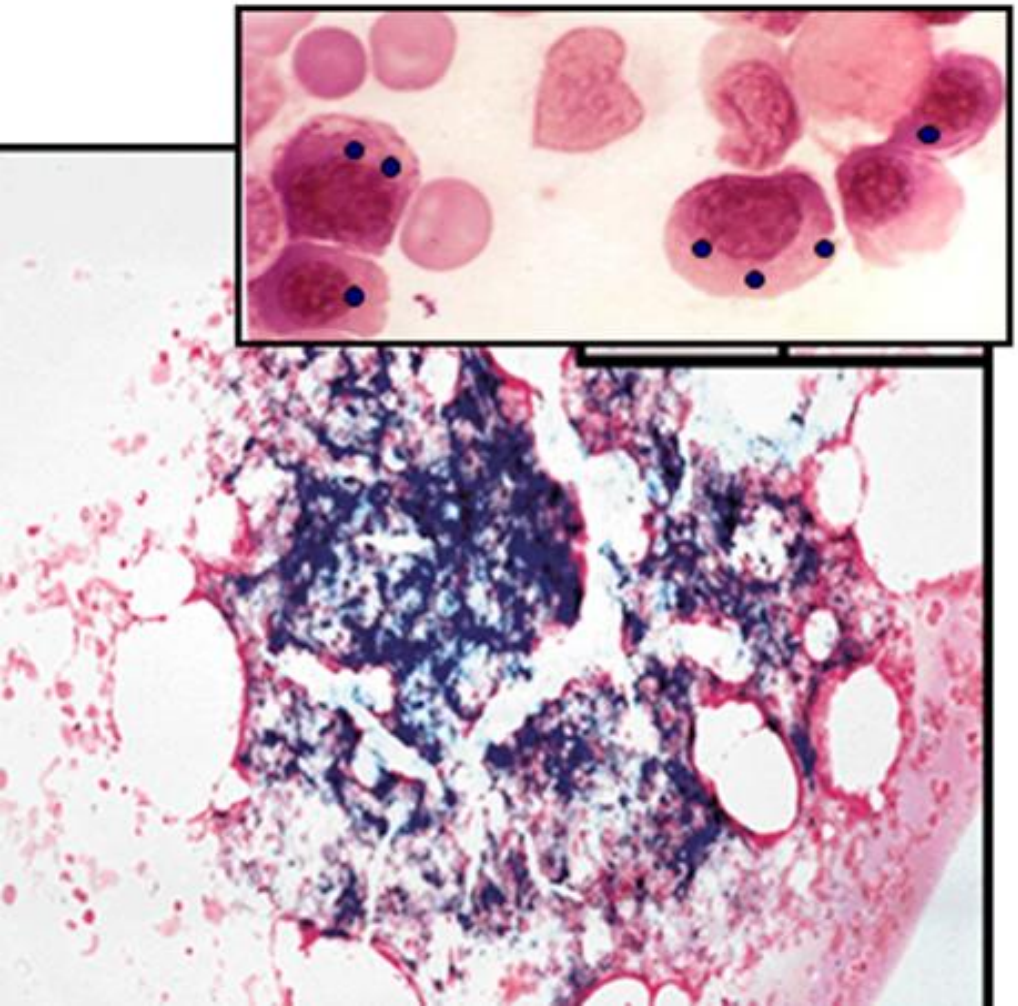



Pencil shaped RBC
ypchromic
Microcytic RBC
Pla
ocytic RBC
Hypochromic RBC
Tear dro
Target shaped RBC

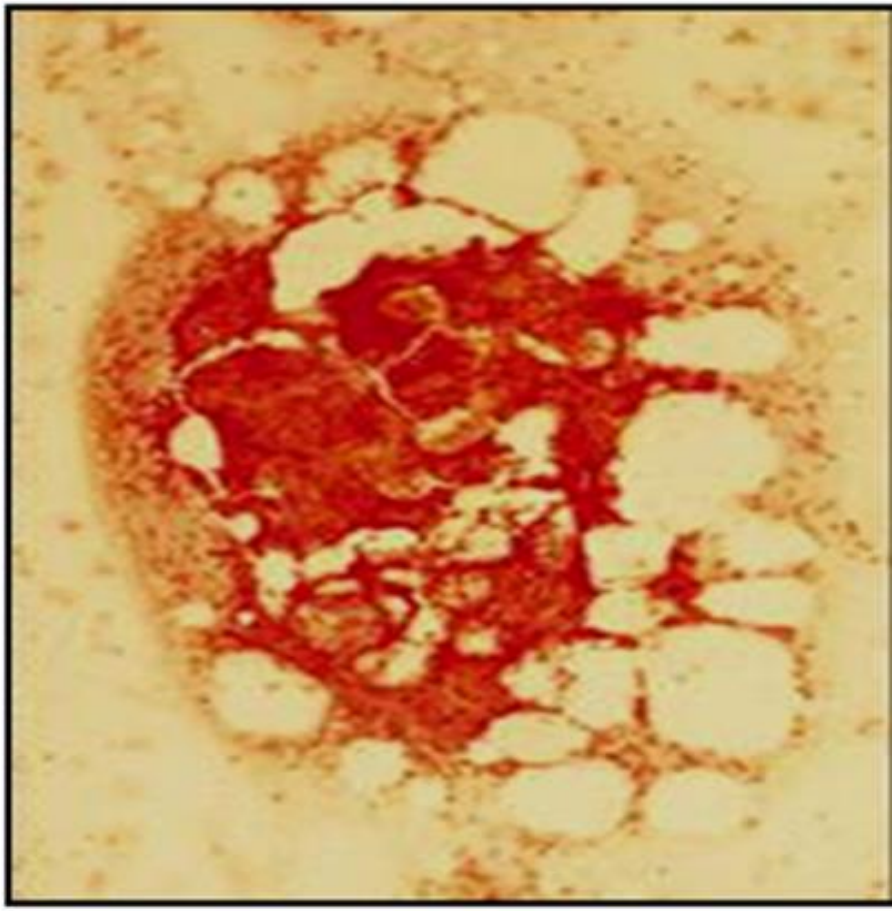
Iron stain on marrow

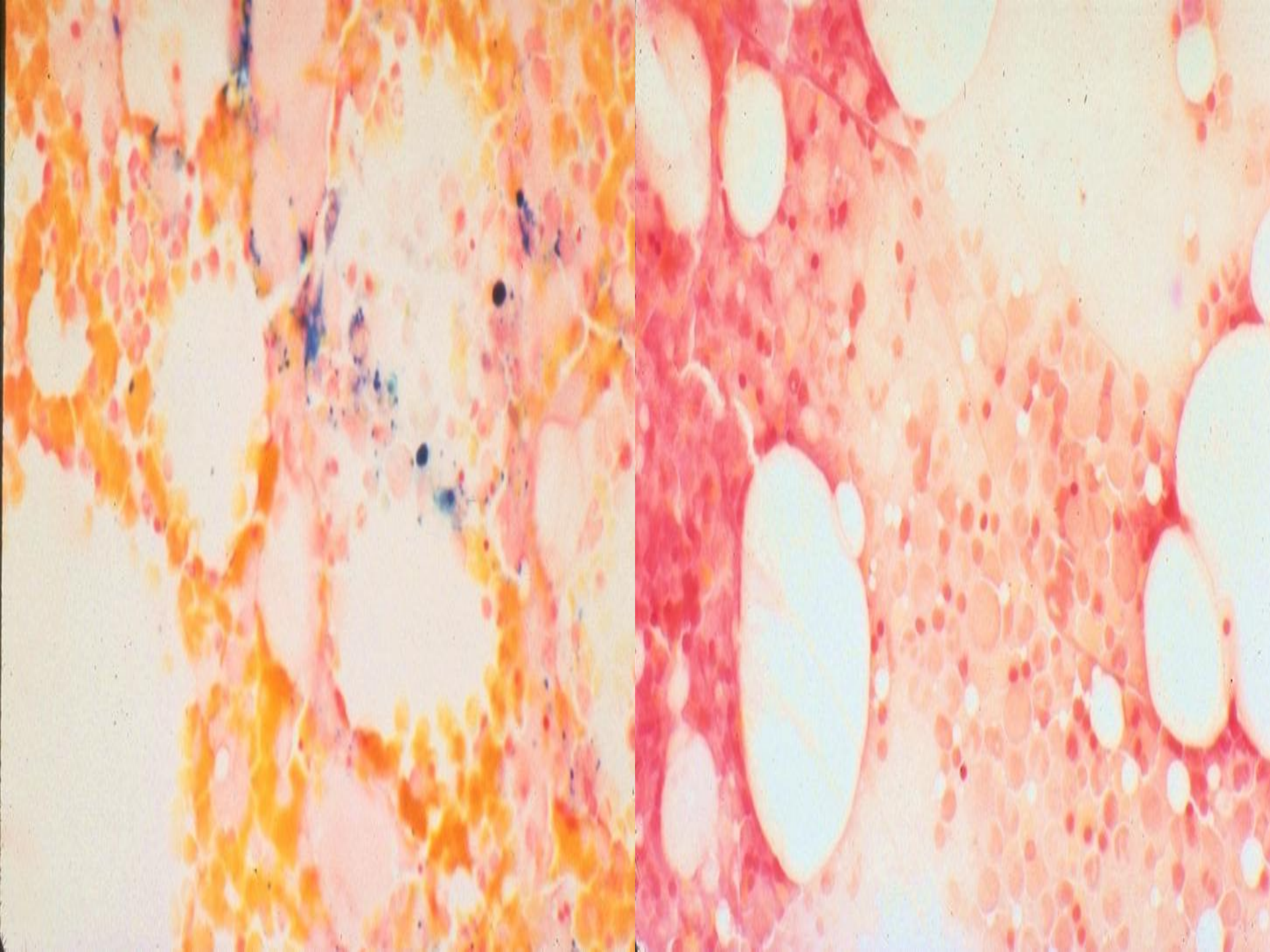
Iron is represented by blue granules

Normal Marrow
Normal storage Iron



Iron deficient marrow
Absent storage iron





2. Biochemical findings:

- ✓ Serum Iron reduced.
- ✓ Total Iron binding capacity increased.
- ✓ S. Iron/TIBC: Transferrin saturation reduced <15%.
- ✓ S.TfR increase.
- ✓ S. Ferritin: reflects storage iron and is classically reduced in IDA (< 15ug/L).

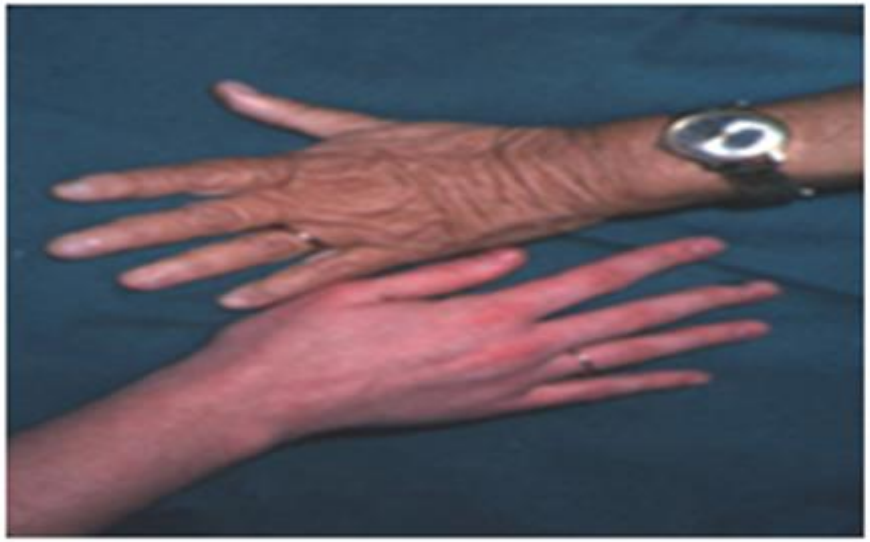
3. Investigations for suspected underlying causes.

Clinical Findings :

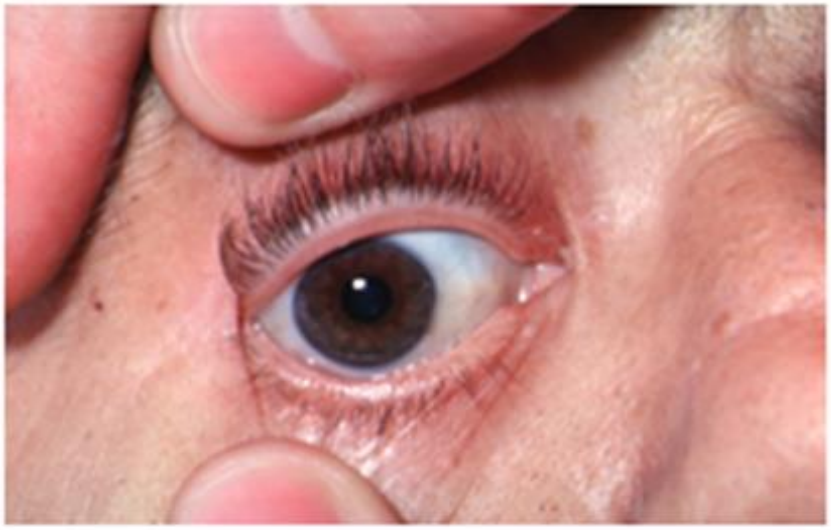
- Early stages: no significant findings.
- As anemia progresses :

1. **Signs and Symptoms of anemia**: Pallor, Fatigue, decrease exercise capacity, shortness of breath.
2. **Mucosal changes** in severe IDA:
   - Mouth soreness (glossitis, smooth red tongue).
   - Spooning of nails (koilonychia)
3. **Pica** (craving to eat unusual substances like dirt, Clay, ice, salt hair or cardboard).
4. No organomegaly relevant to IDA is expected

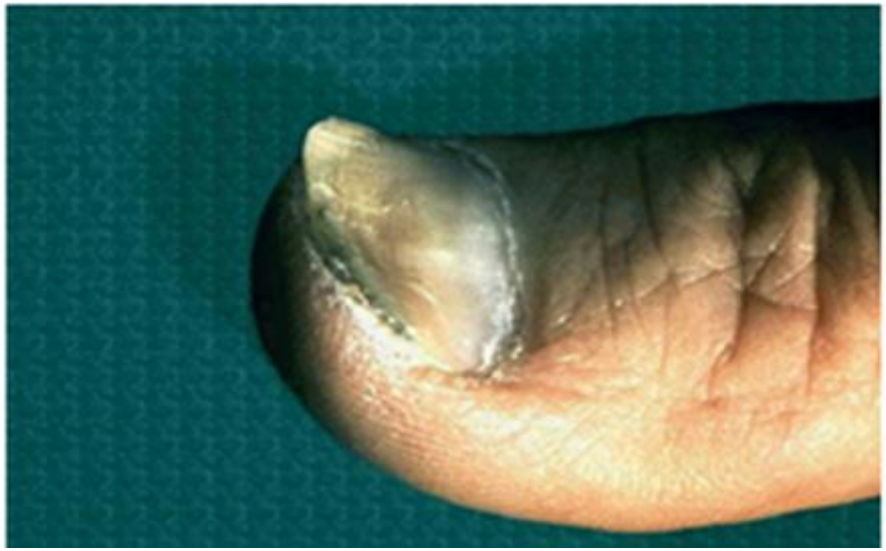
Pallor



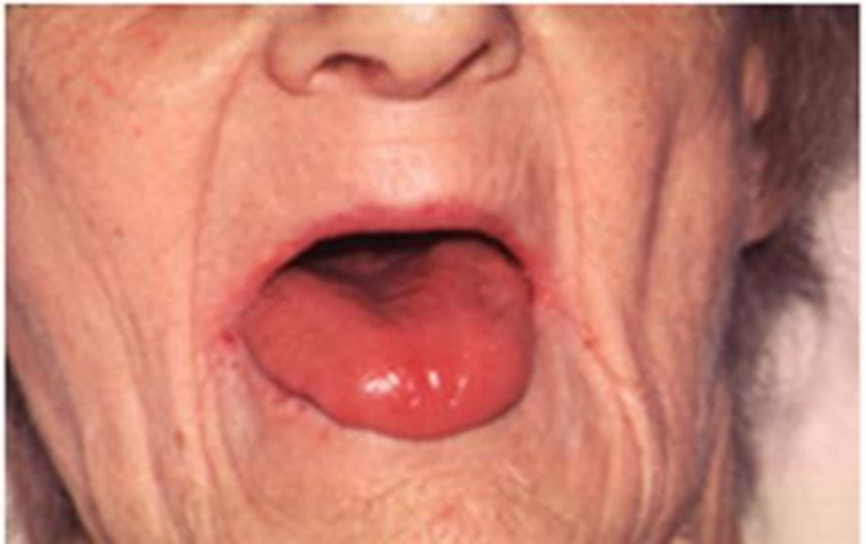
Pale conjunctiva



Koilonychia



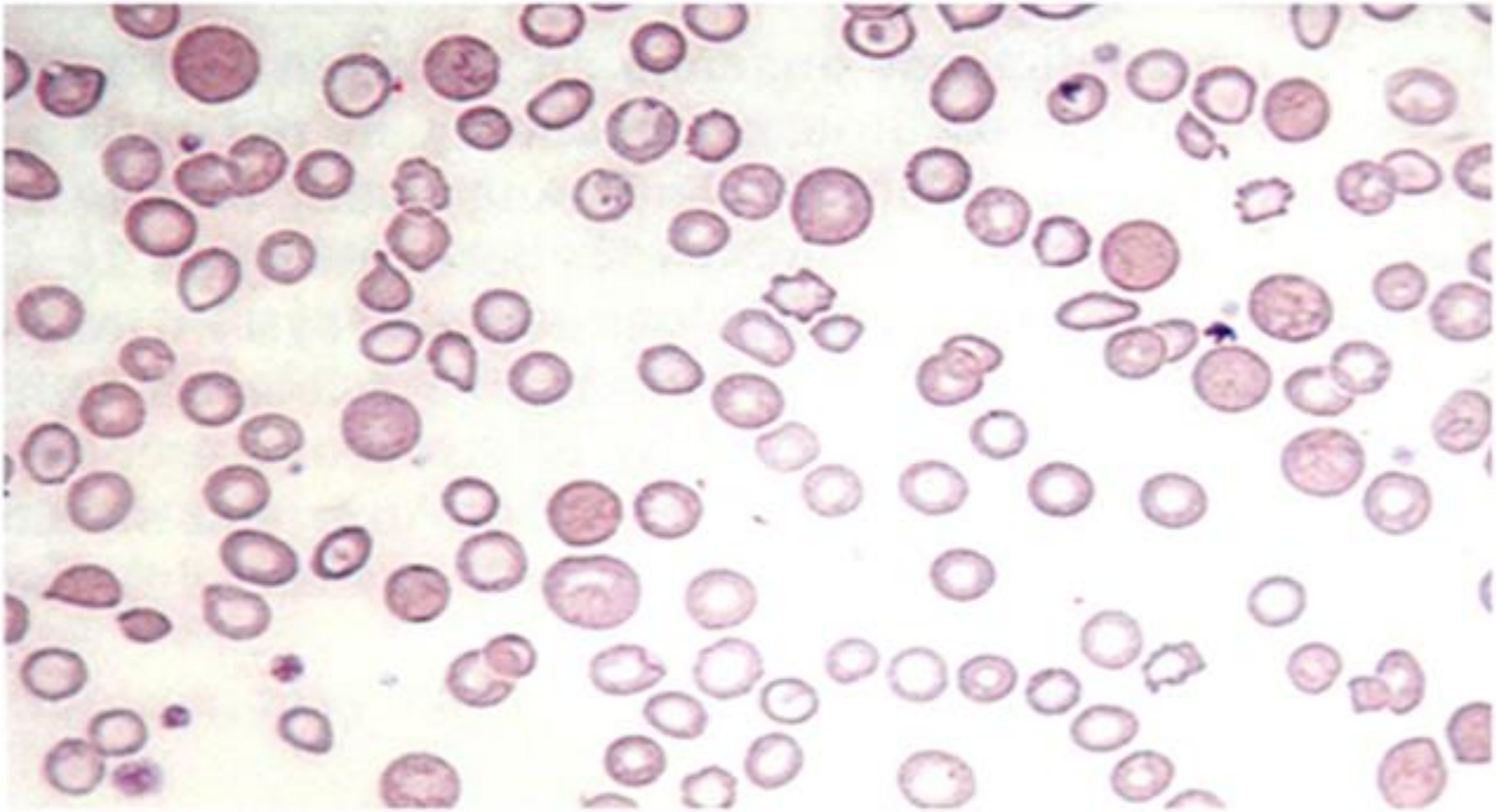
Oral changes



Treatment

- **Treatment of primary causes.**

1. **Oral iron (most effective):**
   - Ferrous sulphate 200 mg (67 mg elemintary iron)
   - Ferrous gluconate 300 mg (37 mg elemintary iron)Dose 100-200mg elemintary iron/day 3-4 time.
   - **Duration** 3-6 months.
   - **Response** by increase Hb (0.5-1gm/wk), retic (peak at 10 days).
   - **Failure to response**: wrong Dx, failure to take the drug, continuous hge, mixed anemias, another cause of anemia, malabsorption.
2. **Parenteral iron:**
   - Sever intolerance oral iron, require rapid restoring, persistent hge, malabsorption are most indications for parenteral iron.
   - Iron sorbitol (jectofer) IM, dextran (inferon) IV.
   - Dose (body wt ×2.3×Hb deficit) + (500-1000 mg).



Dimorphic blood film
in partially treatment iron def. anemia

Table 3.3 Differential diagnosis of hypochromic anaemia.

	Iron deficiency	Chronic disease	Thalassaemia trait (α or β)	Sideroblastic anaemia	IRIDA
MCV/MCH	↓	↓ or N	↓	↓ (congenital) ↑N (acquired)	↓
Serum iron	↓	↓	N	↑	↓
TIBC	↑	↓ or N	N	N	
Transferrin saturation	↓	↓	N	↑	↓
Serum ferritin	↓	N or ↑	N	↑	N
Serum TFR	↑	N	N	N or ↑	↑
Serum hepcidin	↓	↑	N	↓	N or ↑
Bone marrow iron stores	↓	N or ↑	N	N or ↑	↑
Erythroblast iron	↓	↓	N	Ring forms	

IRIDA, iron refractory iron deficiency anaemia; MCH, mean corpuscular haemoglobin; MCV, mean corpuscular volume; N, normal; TFR, transferrin receptor; TIBC, total iron-binding capacity.

Anemia of chronic disease

- Long-standing infections, neoplastic diseases, and chronic inflammatory processes (eg, rheumatoid arthritis, systemic lupus erythematosus) block iron transportation from the storage sites to the bone marrow factory by increase hepcidine level.

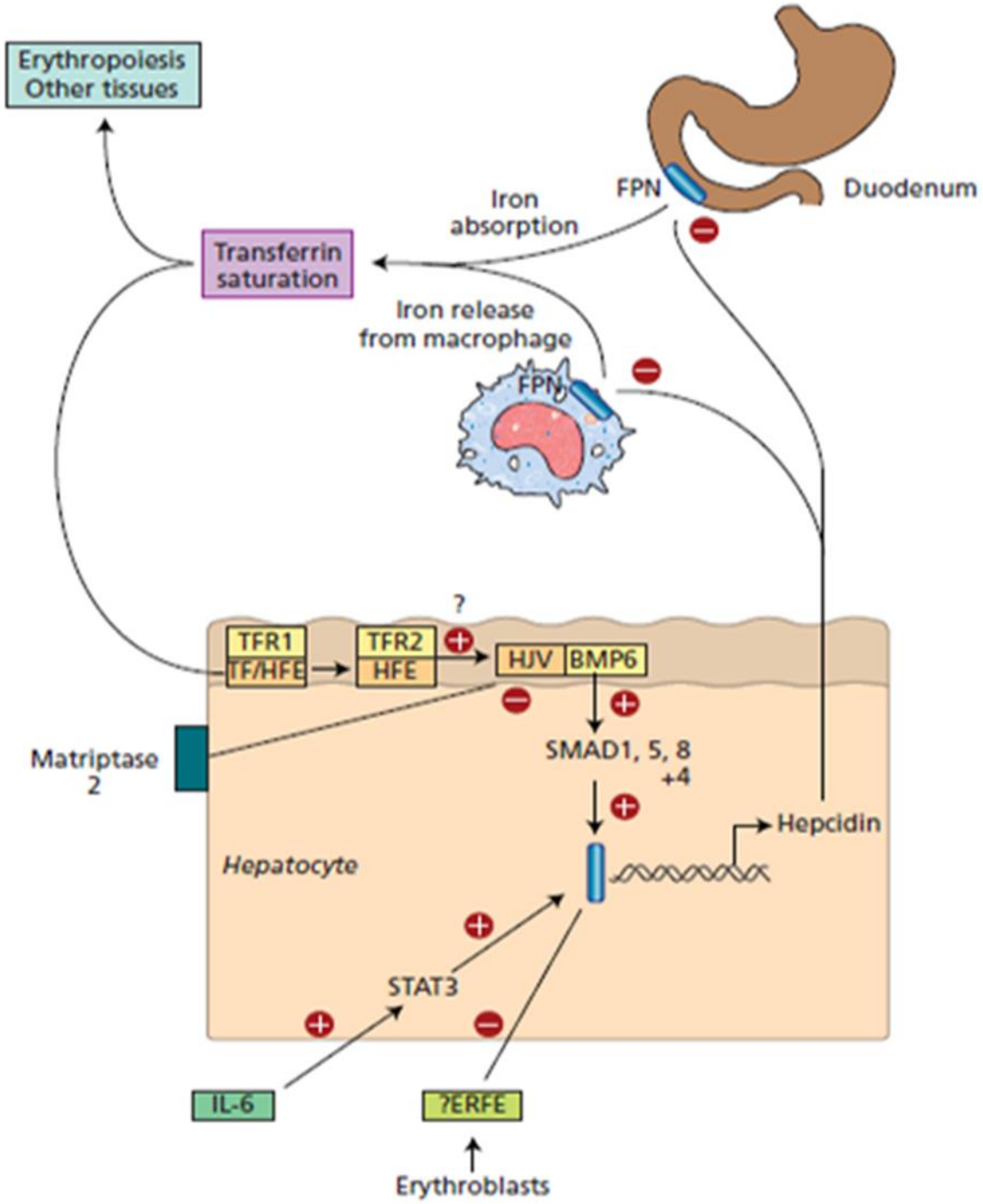


Figure 3.2 Stimulatory and inhibitory signals of hepcidin regulation. Hepcidin, as well as hemojuvelin (HJV), transferrin receptor 2 (TFR2) and HFE, are all produced in the hepatocyte. High plasma iron and inflammation stimulate hepcidin synthesis. This is mediated by SMADs and STAT3, respectively. Conversely, low plasma iron, increased rates of erythropoiesis (including ineffective erythropoiesis) and hypoxia inhibit hepcidin production. This is mediated by matriptase and ERFE. Hepcidin binds ferroportin (FPN), causing its destruction and so inhibits iron absorption and iron release from macrophages into plasma and from intracellular compartments. BMP, bone morphogenetic protein; ERFE, erythroferrone; The ? indicates uncertainty of the ERFE function in humans; GDF-15 may be the human equivalent of ERFE.

Sideroblastic anemias

- characterized by the presence of “ringed” sideroblasts in the bone marrow; associated with hypochromic cells on a peripheral smear.
- May be congenital or acquired
- Acquired sideroblastic anemias are associated with use of antituberculous medications (eg, isoniazid, pyrazinamide14), alcohol abuse, lead poisoning, chronic inflammation .