UCL Université catholique de Louvain

Université partenaire de l'Académie universitaire 'Louvain'

Iron metabolism and medical needs: a view from Academia

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Iron therapy Master Class
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Classification of anemias

type

Regenerative

1. loss of blood (acute)
2. hemolysis

Hyporegeneratives

1. quantitatively insufficient erythropoiesis
   - erythroblastenia *
   - medullar aplasia (e.g., after ceratin drugs)
   - medullar "invasion" (leukaemia…)
2. qualitatively insufficient erythropoiesis
   - insufficient hemoglobin synthesis
     - **iron deficiency or chronic blood losses**
     - **troubles of iron utilization ***
   - insufficient DNA synthesis
     - **vitamin B_{12} deficiency**
     - **folates deficiency**

normocytaire normochrome

microcytaire hypochrome

macrocytaire

* observed in **infectious diseases**, **inflammation**, and **cancer** (chronic situations)

What does the doctor need to look for in patients ?

TABLE 2 *Some symptoms of anaemia*

Part of body affected	Compensatory mechanism	Dysfunction[a]
Brain		Fatigue/tiredness, headaches, dizziness, difficulty thinking/concentrating, depressed mood
Eyes		Retinal damage
Heart	Rapid pulse, palpitations	Angina
Lungs	Rapid breathing, breathlessness	In severe cases, worsened breathlessness from pulmonary oedema secondary to heart failure
Kidneys		Water retention
Gut	Loss of appetite	Indigestion, irregular bowel movements, failure to absorb nutrients from food
Muscles/legs		Fatigue, reduced exercise capacity, swelling secondary to water retention (due in turn to kidney and heart failure)
Skin	Pallor, feeling cold	Brittle/broken nails
Reproductive organs		Increased menstrual bleeding, loss of periods, impotence, decreased libido

[a] The clinically important effects are magnified if anaemia develops rapidly or organs are compromised and unable to work at increased capacity, e.g. coronary artery disease for symptoms associated with dysfunction of the heart.

Where is iron stored, and what for ?

Organ / Cells	amount	function
Red blood cells	1.8 g	**O_2 transport**
RES macrophages	0.6 g	iron storage
Liver	1.0 g	**O_2 metabolism** / storage
Bone marrow	0.3 g	**O_2 metabolism** / storage
Muscles (myoglobin)	0.3 g	**O_2 metabolism**
Other tissues[8]	0.1 g	**O_2 metabolism**
Transferrin	0.003 g	iron transport

- Iron stores are **low** compared to functional iron hemoglobin / myoglobin …
- Circulating iron is **very low** in quantity …

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Organ / Cells	ion
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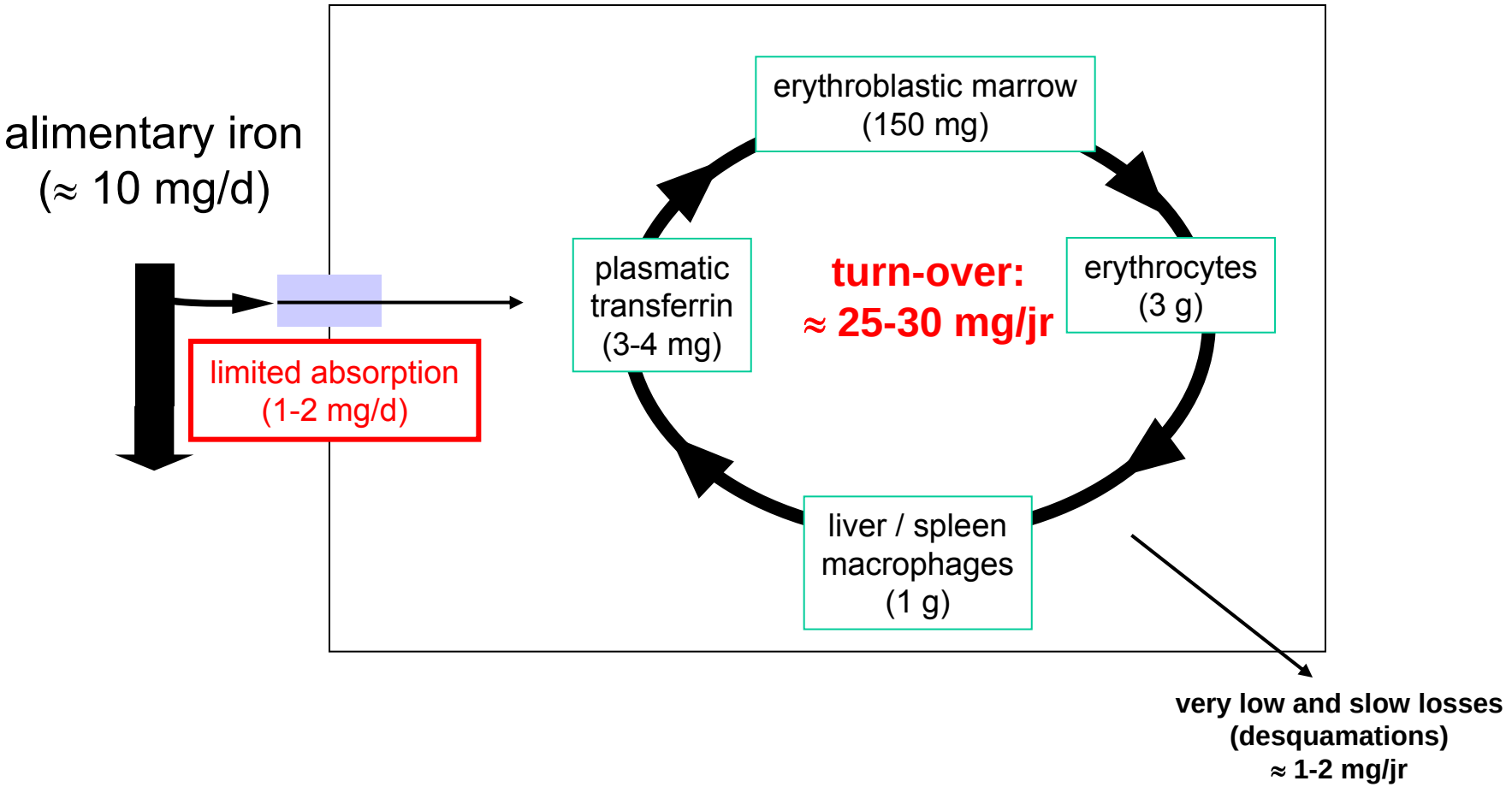
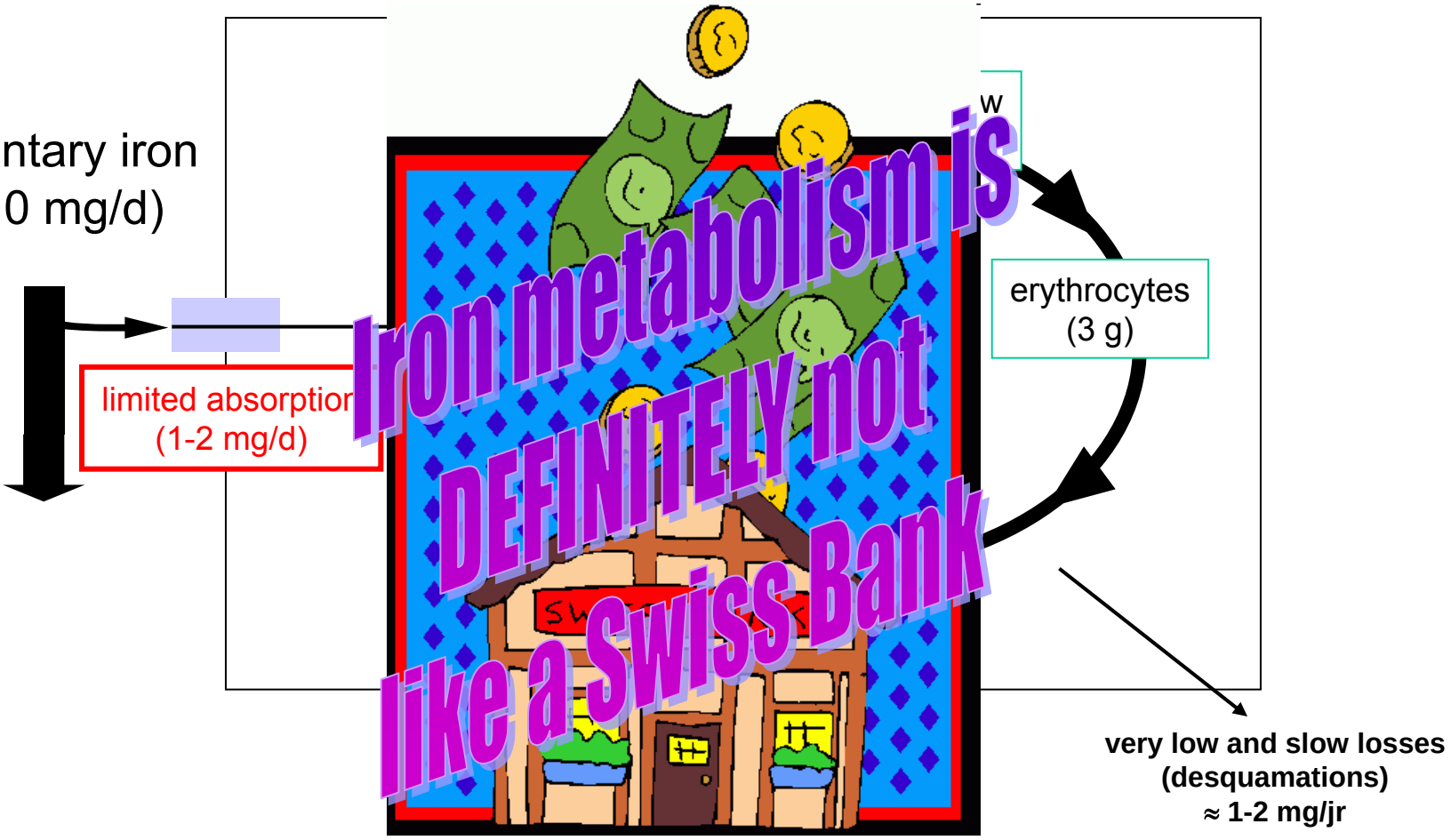
Movements of iron into, within, and out of the body…



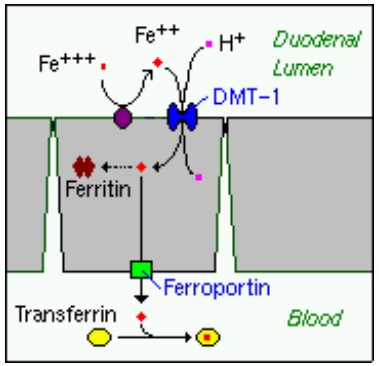
The **in and out** movements of iron are **very limited** compared "in body" turnover …

Movements of iron into, within, and out of the body…



The **in and out** movements of iron are **very** limited compared "in body" turnover …

Absorption of iron: 1. intestinal control



- Iron homeostasis is regulated at the level of intestinal absorption
- Iron is absorbed by villus enterocytes in the proximal duodenum
- Efficient absorption requires an acidic environment (antacids or other conditions that interfere with gastric acid secretion can interfere with iron absorption)
- Ferric iron (Fe^{+++}) in the duodenal lumen is reduced to **Fe^{++}** * through the action of a brush border ferrireductase, and is cotransported with a proton into the enterocyte via the divalent metal transporter DMT-1 (which also transports many divalent metal ions.

- Inside the enterocyte, iron follows one of two major pathways
  - Iron abundance states: iron within the enterocyte is trapped by incorporation into ferritin and hence, not transported into blood. When the enterocyte dies and is shed, this iron is lost.
  - Iron limiting states: iron is exported out of the enterocyte via a transporter (ferroportin) located in the basolateral membrane

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* favored by co-administration of ascorbic acid (vitamin C)

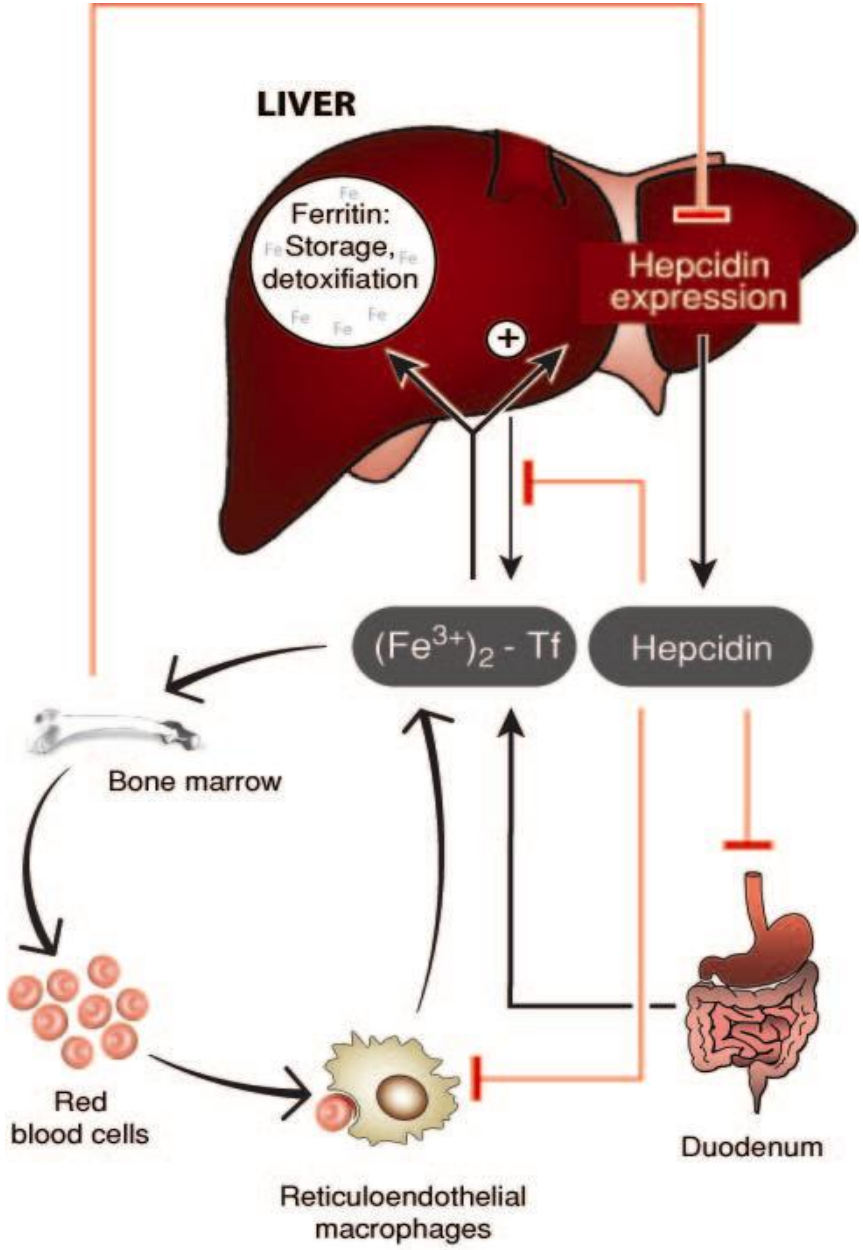
http://arbl.cvmbs.colostate.edu/hbooks/pathphys/digestion/smallgut/absorb_minerals.html

Iron absorption and mobilization: 2. role of hepcidin

Systemic iron homeostasis:

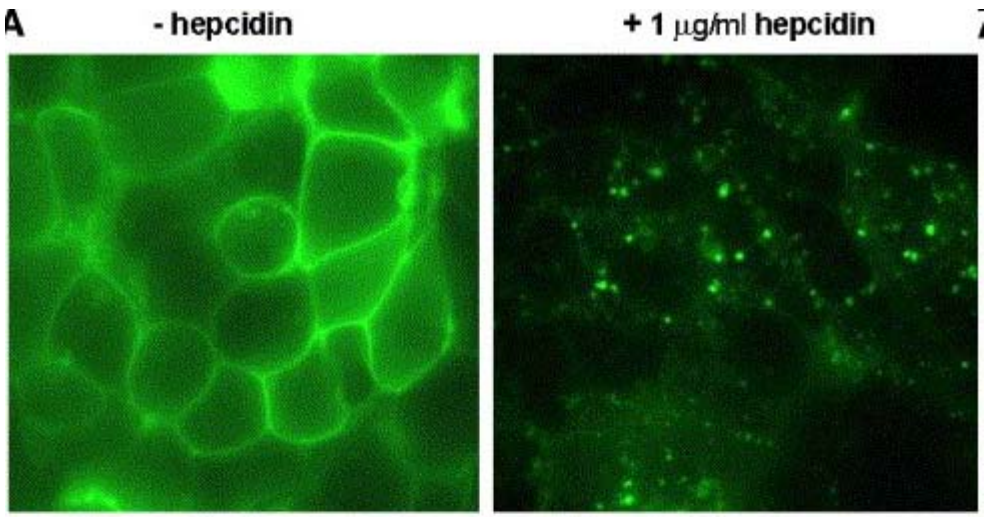
- Hepcidin controls the transferrin iron saturation by inhibiting iron efflux mainly from duodenal enterocytes and macrophages but also from hepatocytes.
- Hepcidin synthesis is positively regulated by the iron stores and negatively regulated by erythropoietic activity.

Note: the signal that regulates hepcidin expression through erythropoiesis, anemia and hypoxia is still unknown, but **inflammation may increase its production**



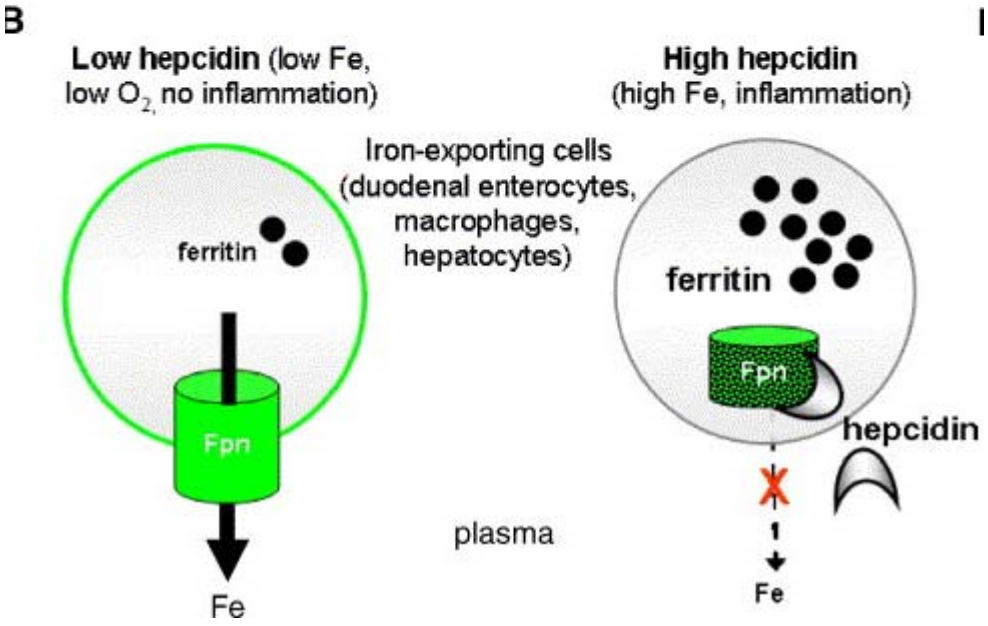
Muckenthaler MU, et al. 2008.
Annu. Rev. Nutr. 28:197–213.

Hepcidin "turn off" * the iron export system



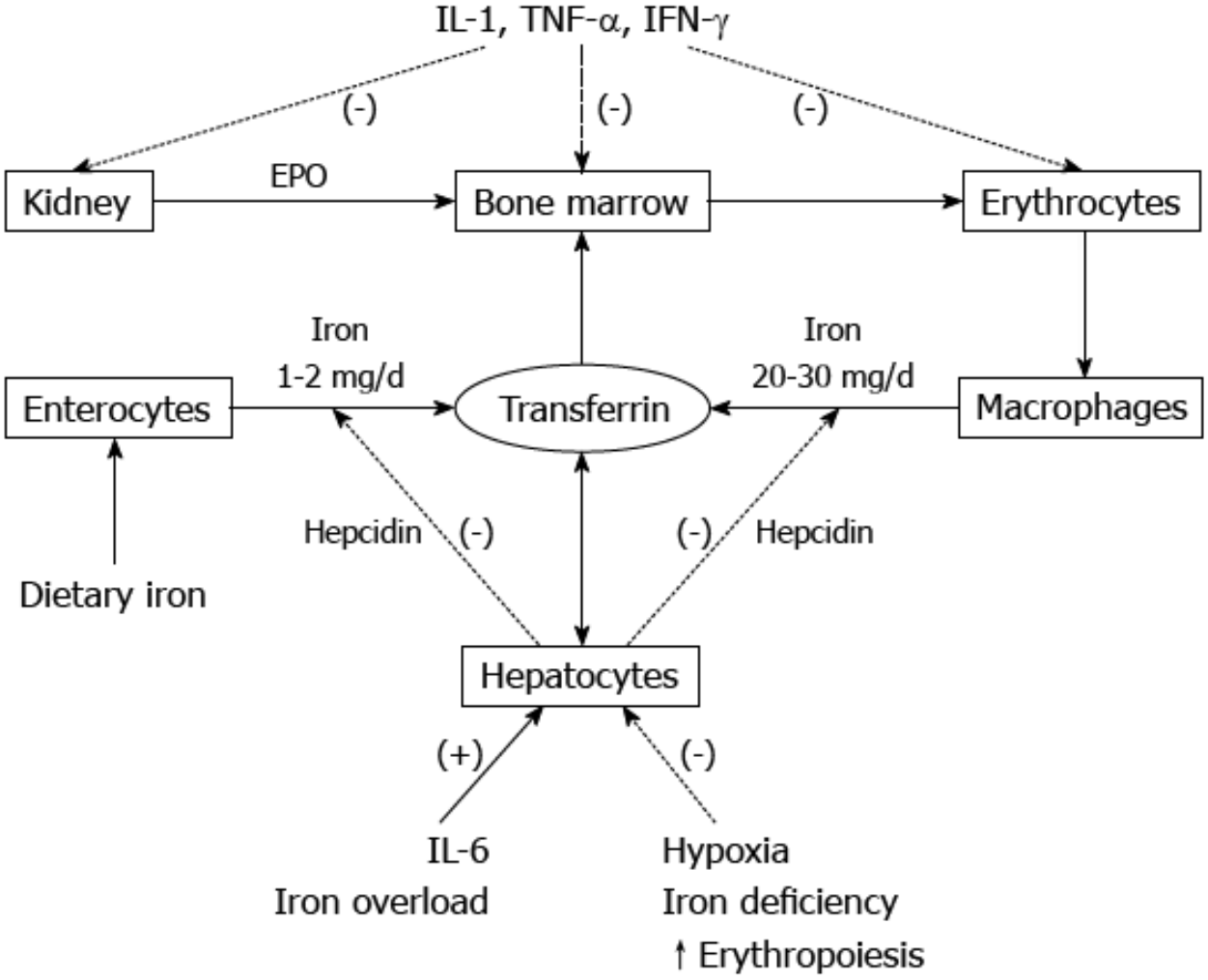
A. **before hepcidin treatment.**

B. **after hepcidin treatment: the ferroportin has been internalized leading to decreased cellular iron efflux.**



Ganz & Nemeth, Biochim Biophys Acta. 2006;1763:690-9

Why do inflammation cause anemia ?



Effects of inflammation on erythropoiesis and iron homeostasis in mammals.

(-): Negative effect; (+): Positive effect.

Munoz et al. World J Gastroenterol 2009; 15:4617-4626

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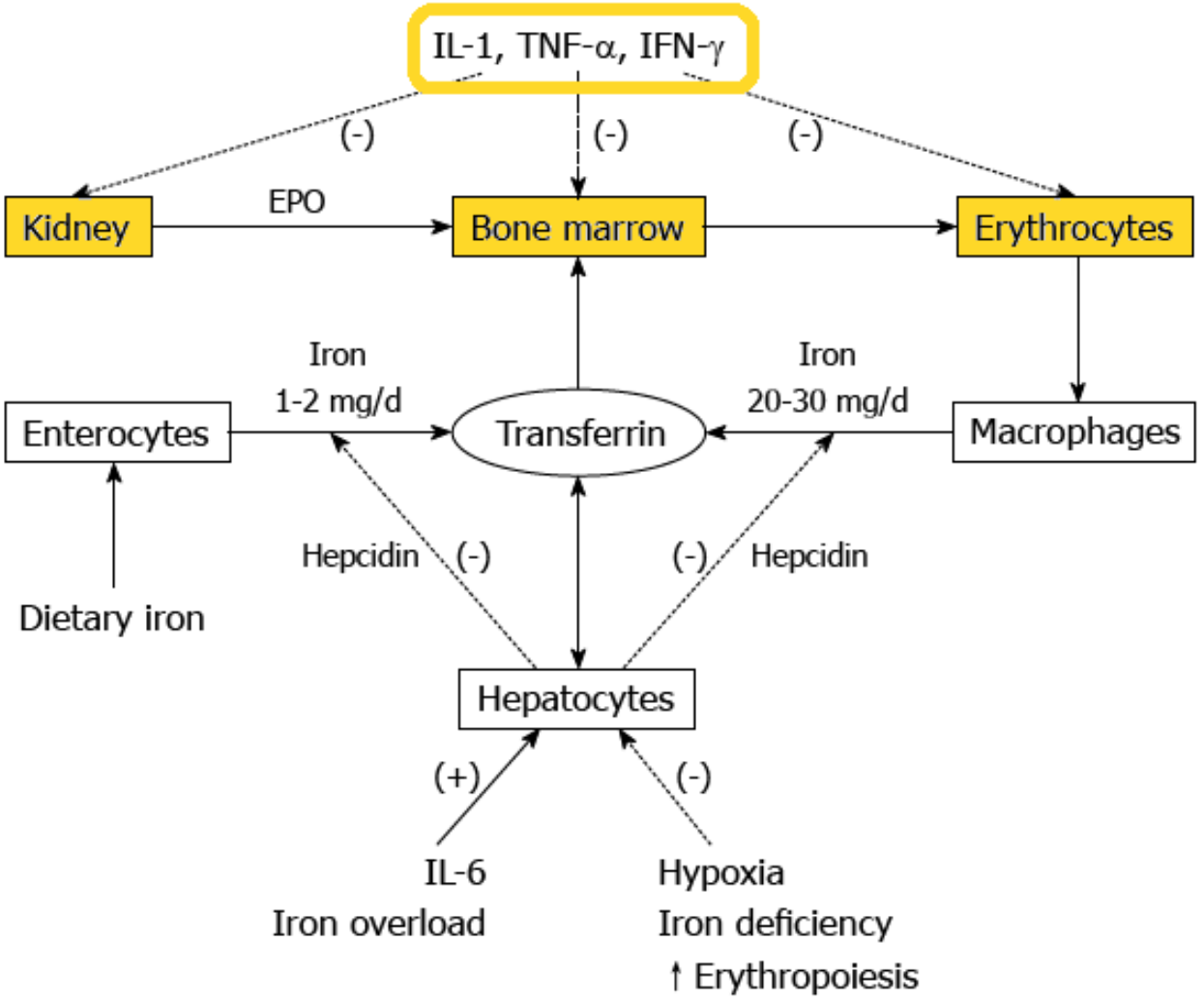

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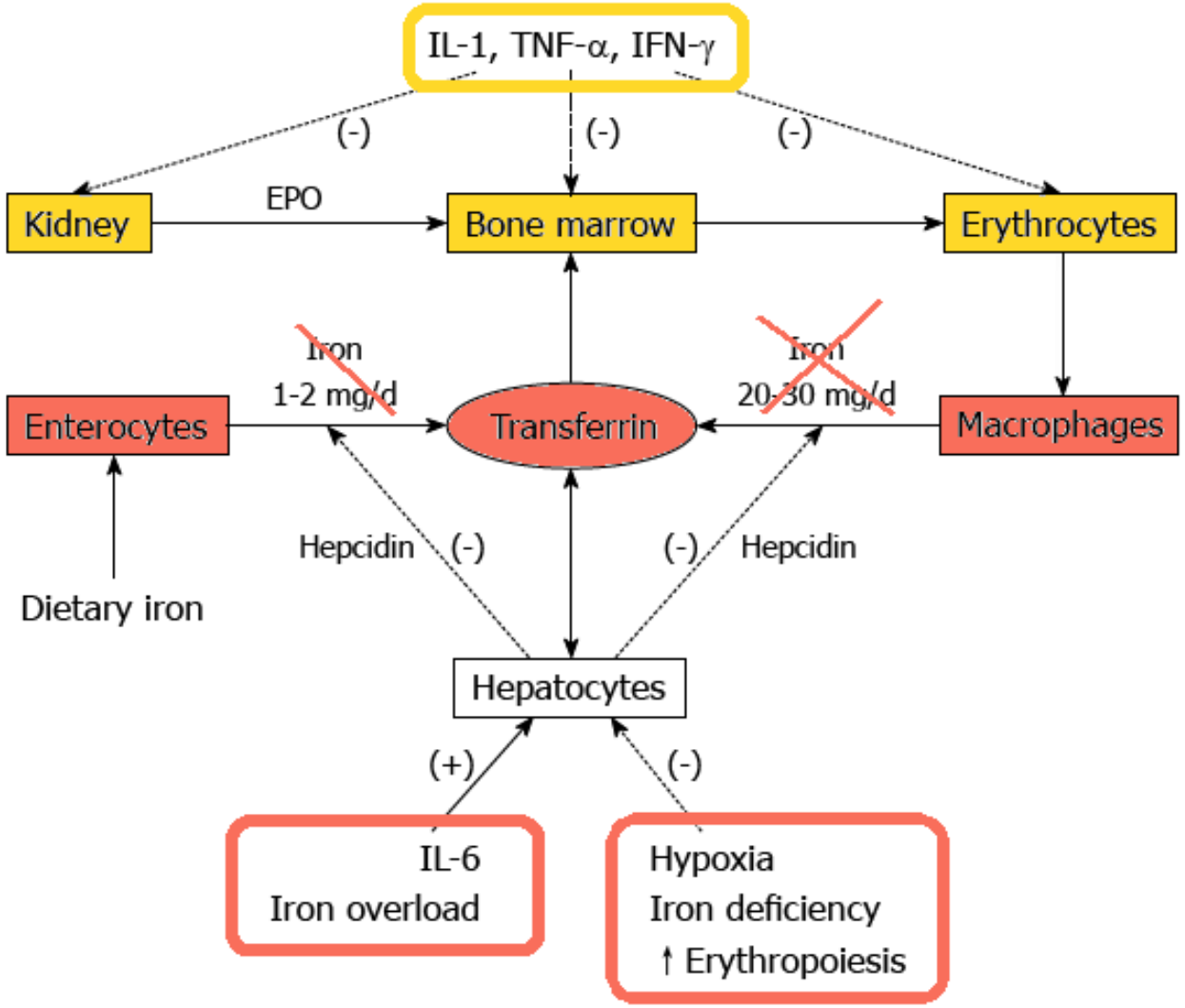

Effects of inflammation on erythropoiesis and iron homeostasis in mammals.

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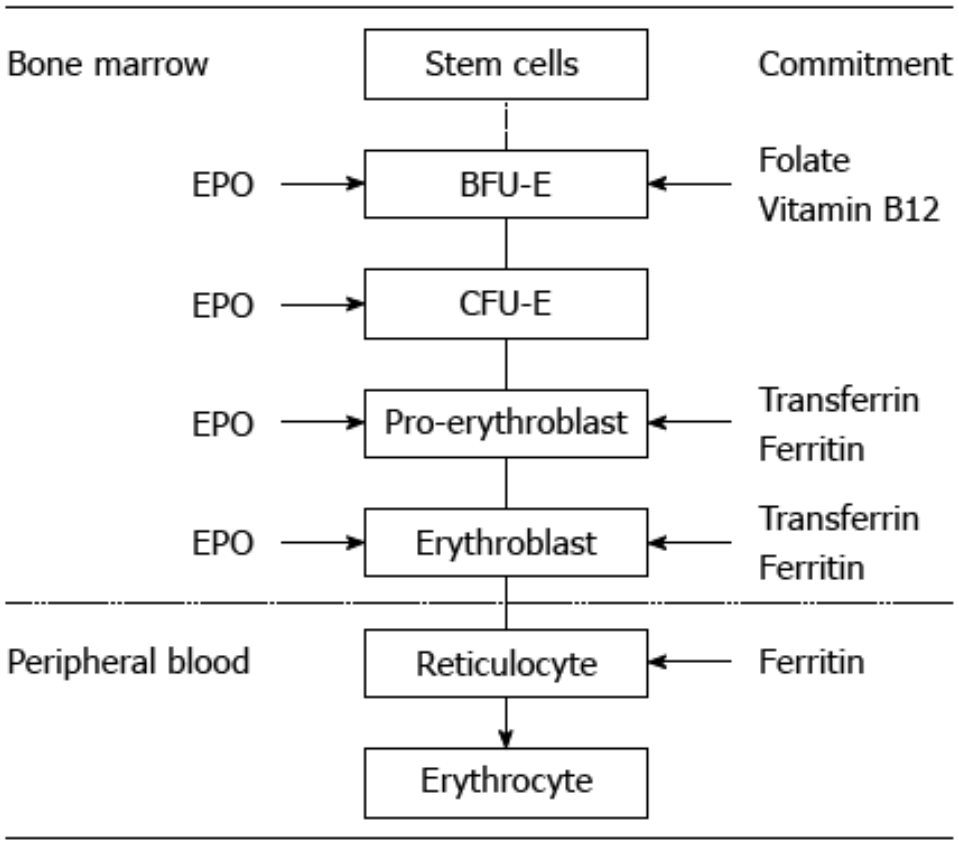
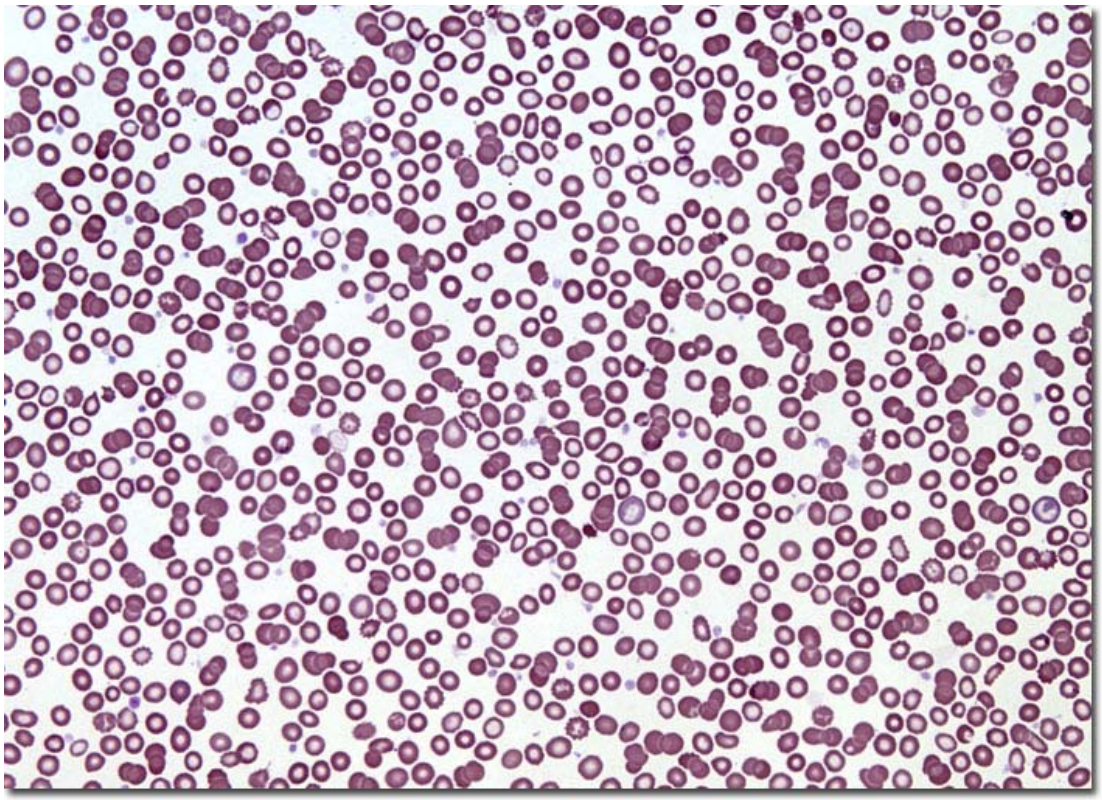
When do erythrocytes need iron ?



for the final maturation of red blood cells
(synthesis of hemoglobin)

Figure 1 Major stages of human erythropoiesis showing the point of commitment, the period of EPO dependence and the requirements for essential nutrients. BFU-E: Burst-forming unit-erythroid; CFU-E: Colony-forming unit-erythroid; EPO: Erythropoietin.

Anemia



Anemia is a condition characterized by a bodily insufficiency of red blood cells, hemoglobin, or a combination of the two. **A most common form is iron deficiency anemia**, related to a paucity of the mineral iron, which the body requires to produce hemoglobin and transport oxygen.

Without enough oxygen circulating in the body, symptoms such as **extreme fatigue**, **pallor**, **weakness**, **lightheadedness**, **shortness of breath**, and **cold extremities** may develop. Other possible signs of iron deficiency anemia include brittle nails, poor appetite, increased susceptibility to infection, headache, swelling and soreness of the tongue, and cracking of the sides of the mouth, though mild cases are sometimes asymptomatic.

http://www.microscopyu.com/galleries/pathology/irondeficiencyanemiaexlarge.html

Iron deficiency anemia: who is at risk ?

- nutrition deficiencies
  - lack of animal iron or "poor" quality nutrition
- pregnant women
  - fetal reserves building
- children
  - growth (young children)
  - ill-adapted nutrition (adolescents; young women)

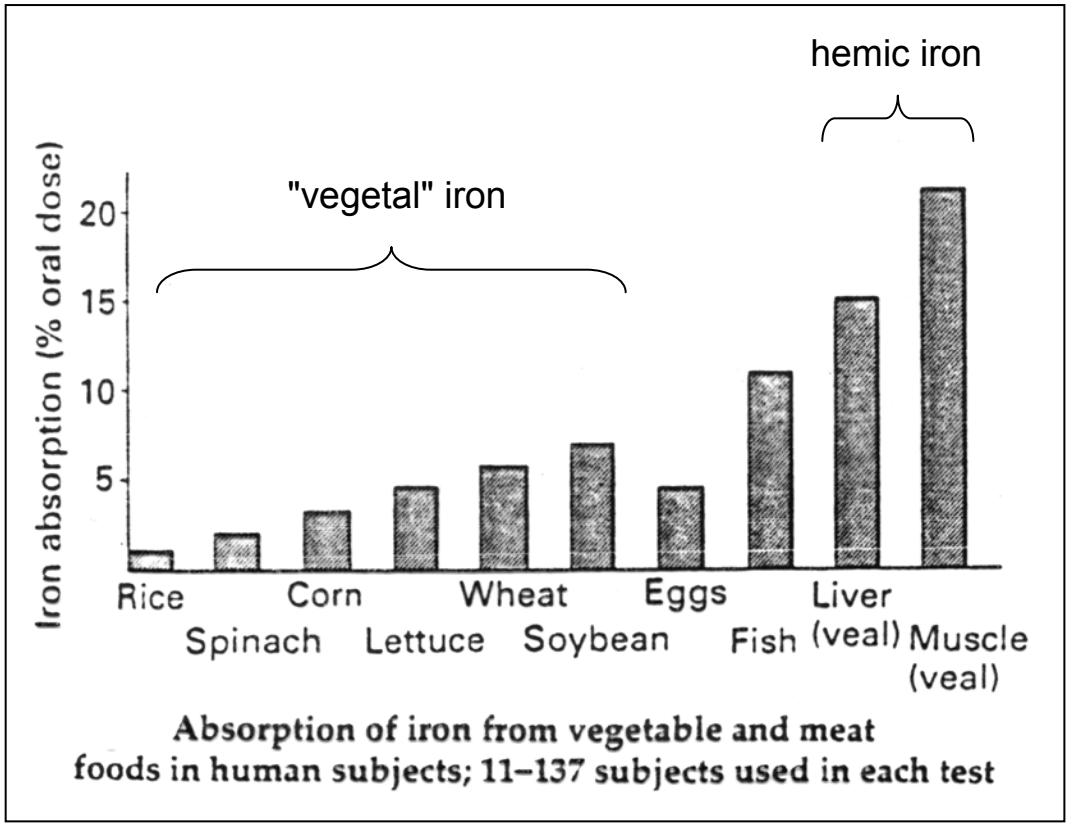
➔ improve nutritional status

- aged patients with decreased
  - medullar reserve
  - hormonal response to erythropoietic stimulants
  - alimentary supply
- acute blood loss
  - surgery
- cancer / inflammation / infections
  - "resistance" to erythropoietic stimuli

➔ intervene !

http://www.microscopyu.com/galleries/pathology/irondeficiencyanemiaexlarge.html

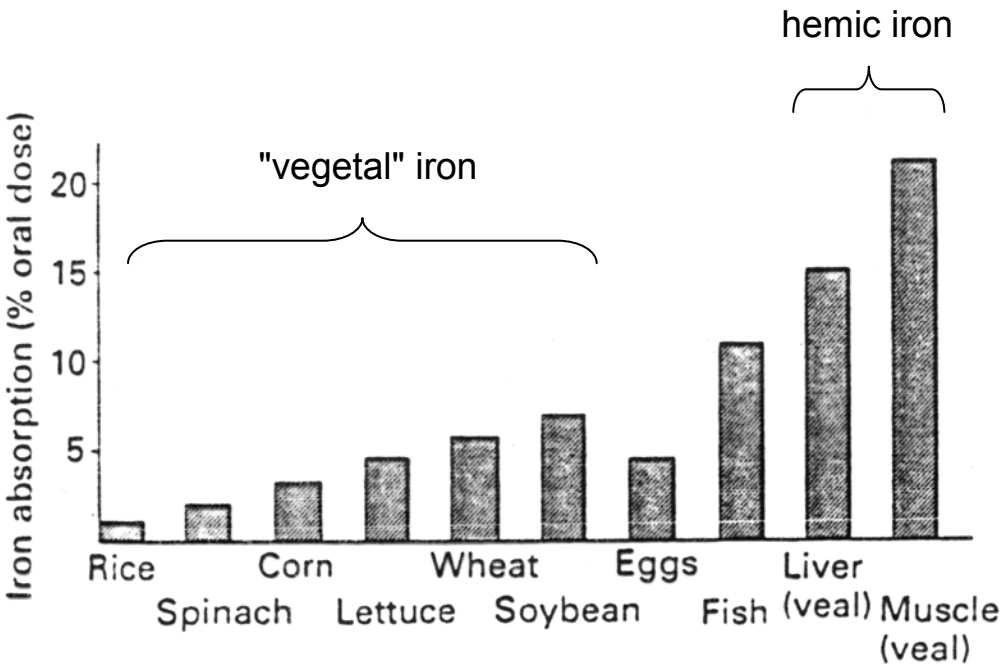
Alimentary supplies



Absorption of iron from vegetable and meat foods in human subjects; 11–137 subjects used in each test

This guy is wrong !

Alimentary supplies



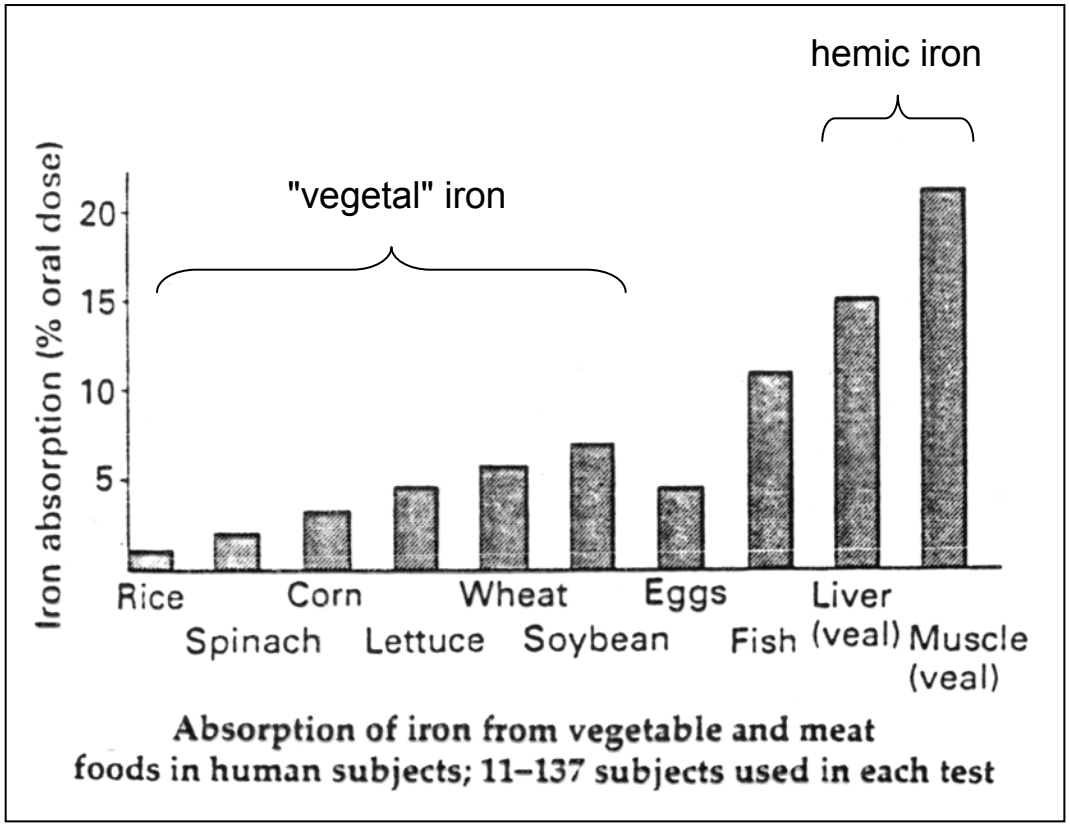
Absorption of iron from vegetable and meat foods in human subjects; 11–137 subjects used in each test

Table 28.5 **Iron content of alcoholic beverages**

Beverage	*Iron content (mg/l)*
US beer	0.1
Gin, whisky	0.6
US wines	2.3–2.6
Red and white French wines	6.2
Cider and wine from Rennes (France)	10–16

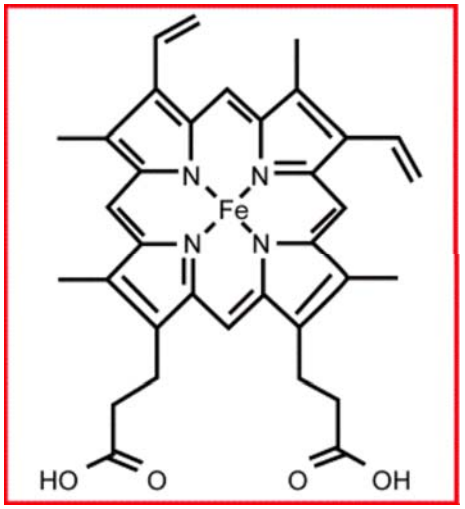
From R.A. McDonald (1963) *Arch. Intern. Med.*, **112**, 184.

Alimentary supplies



Absorption of iron from vegetable and meat foods in human subjects; 11–137 subjects used in each test

What you need (for optimal bioavailability) is this:



myoglobin **hemoglobin**

old but useful publication ➡

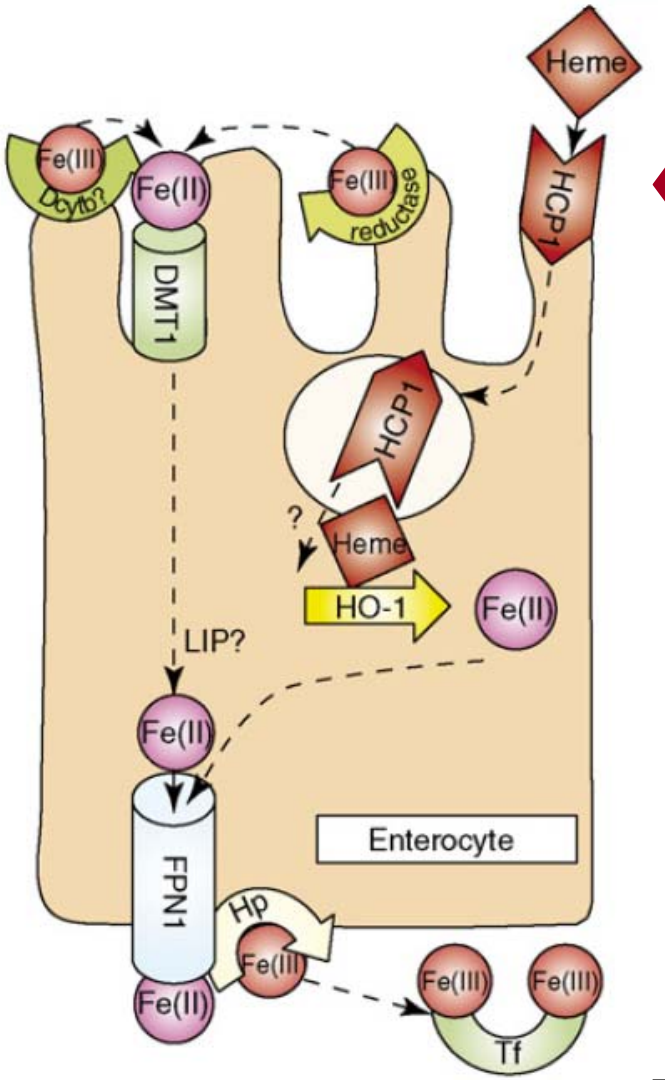
Food Iron Absorption:
A Comparison of Vegetable and Animal Foods

By M. Layrisse, J. D. Cook, C. Martinez, M. Roche, I. N. Kuhn, R. B. Walker and C. A. Finch

Iron absorption measurements have been made in 131 individuals relating the absorption of nine different foods tagged biosynthetically with radioiron. Relatively low absorption, ranging from 1.7–7.9, was found with wheat, corn, black beans, lettuce and spinach. Higher values of from 15.6–20.3 were observed with soybeans, fish, veal and hemoglobin.

Blood, Vol. 33, No. 3 (March) 1969, 430

Why is hemic iron more bioavailable ?



because of the presence of a specific heme-transporter at the level of the intestinal cell villi

Dunn et al. Trends in Cell Biol 2006; 17: 93-100

Oral iron with pharmaceutical preparations …

All have a **poor bioavailability** (non hemic iron…)

- May help if … you have a lot of time *
  thus, not in acute situations
  (ascorbic acid may help …)
- treatment is ALWAYS long (3-6 months!!)

All have **several undesirable effects** (you MUST warn the patient !!) due to presence of **large amounts of free iron** (that will not be reabsorbed)

- irreversible teeth staining
- diarrhea or constipation,
- blackened stools (with persistent stains on clothes)
- risk of ulcers (Iron sulfate) **

Do **NOT** administer with drugs that may be **complexed** by dicationic or tricationic iron (diphosphonates, levodopa, fluroquinolones, tetracyclines, …) or which can reduce iron bioavailability (antacids, phosphates, calcium salts, …)

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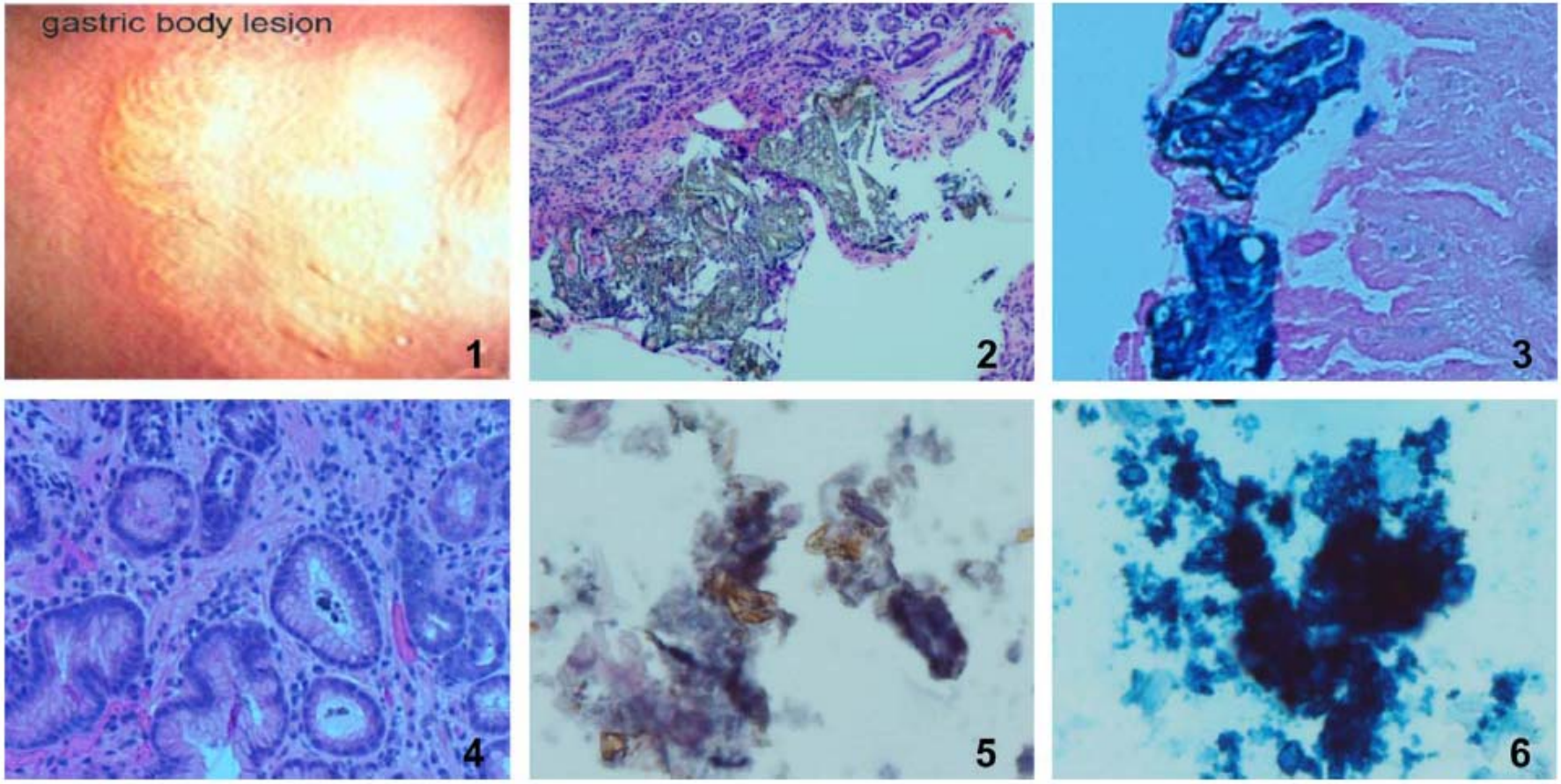
* typical time to recover from a 300 ml blood loss: 1-2 months

** see next slides

Iron sulfate and gastric ulcers…



Figs. 1–6. 1. Esophagogastroduodenoscopy: pale, villous appearing flat lesion along the lesser curvature of gastric body. **2**. Gastric biopsy: crystalline iron deposition overlying gastric mucosa with fibrosis and chronic inflammation (H&E, 200 ×). **3**. Gastric biopsy: Prussian blue stain highlights the crystalline iron deposition (Prussian blue, 200 ×). **4**. Gastric biopsy: iron deposition in gastric glands (Prussian blue, 400 ×). **5**. Ferrous sulfate tablet: iron tablet material shows crystalline appearance (HE, 400 ×). **6**. Ferrous sulfate tablet: Prussian blue stain of iron tablet material (Prussian blue, 400 ×) (for interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Zhang et al., Pathol Res Pract. 2009;205:579-81

Iron sulfate and esophageal ulcers…

Iron-induced esophageal ulceration

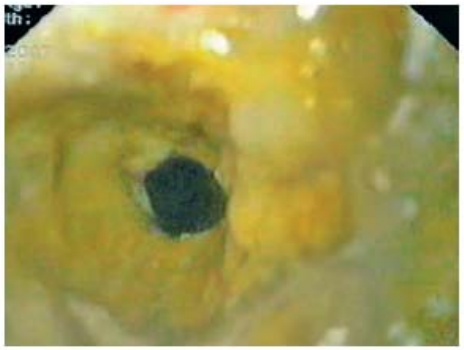


Fig. 1 Upper endoscopy at day 1 revealed a black-brown, ulcerated and necrotic lesion, just below the upper esophageal sphincter.

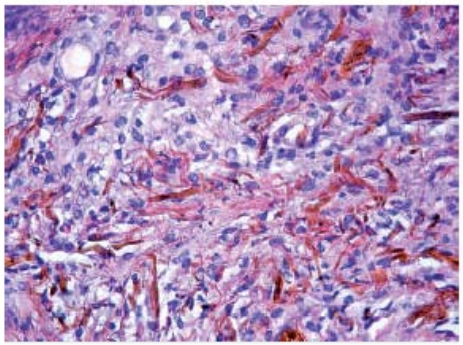


Fig. 2 Granulation tissue from the area with ulcerated esophagitis containing abundant brown crystalline material (hematoxylin and eosin, × 400).

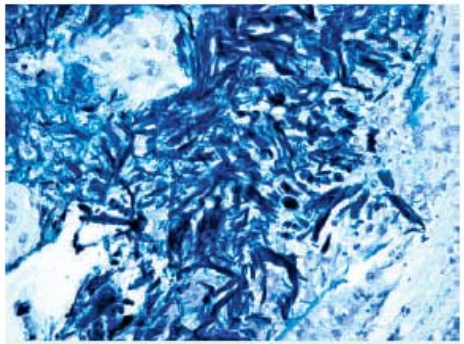


Fig. 3 Positive blue staining of the crystalline material with Perl's iron stain (× 400).

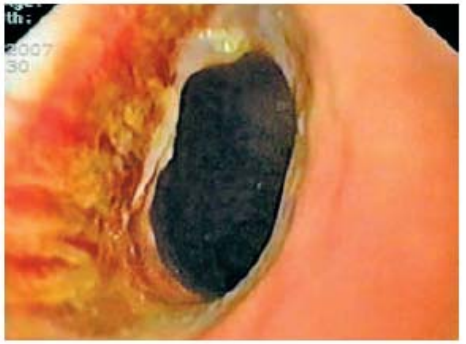


Fig. 4 Upper endoscopy at day 8 showing the progressive resolution of the lesion, with a brown pigmentation and no necrosis.

Areia et al., Endoscopy. 2007; 39 Suppl 1:E326

Oral Iron preparations ..

Fer gluconate

Losferron (Grünenthal)

[fer gluconate]
compr. efferv. (séc.)
30 x 695 mg Rx € 8,83
60 x 695 mg Rx € 16,78
(80 mg Fe^{++})

Polysaccharate ferrique

Ferricure (Trenker)

[polysaccharate ferrique complexe]
caps.
28 x 326 mg Rx € 10,40
56 x 326 mg Rx € 17,06
(150 mg Fe^{+++})
sol.
60 ml 225 mg/5 ml Rx € 9,11
200 ml 225 mg/5 ml Rx € 21,30
(100 mg Fe^{+++})

Fer sulfate $7H_2O$

Fero-Grad 500 (Pharma Logistics)

[acide ascorbique 500 mg + fer sulfate 7H2O 525 mg]
compr. (lib. prolongée)
30 Rx € 7,79
(105 mg Fe++)
60 Rx € 14,79

Fero-Gradumet (Pharma Logistics)

[fer sulfate 7H2O]
compr. (lib. prolongée)
30 x 525 mg Rx € 4,46
60 x 525 mg Rx € 8,05
(105 mg Fe^{++})

Much of this iron is not absorbed !

Association fer - acide folique

Gestiferrol (Kela)

[acide folique 0,5 mg + fer fumarate 200 mg]
compr. (séc.)
36 Rx € 4,61
(65 mg Fe^{++})
Posol: 1 compr. p.j.

When iron is more urgently needed than can be obtained by oral route ?

- **intolerance or low adherence to oral preparations**
  (up 1/5 of all patients [Kulliggs et al. Alim. PharM; Ther. 2006; 24:1507-1523)

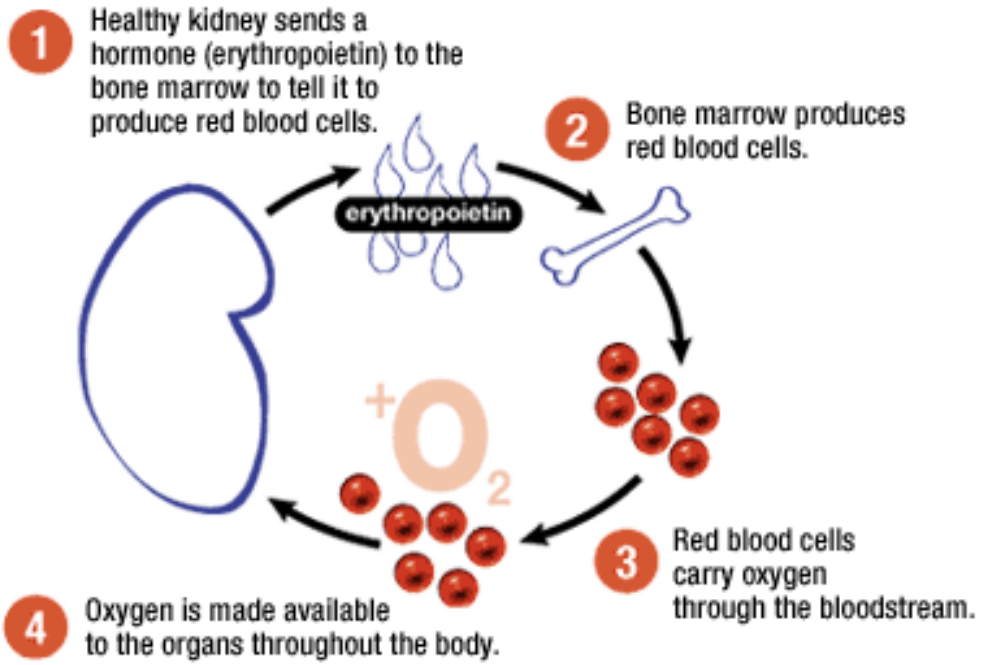
- **acute blood loss**
  - surgical interventions and accidental hemorragea
  - post-partum

- **diseases associated with disturbance of iron absorption and/or utilization**
  - inflammatory bowel disease
  - congestive heart failure
  - chronic kidney disease
  - cancer-related anemia

  } in association with erythropoietin

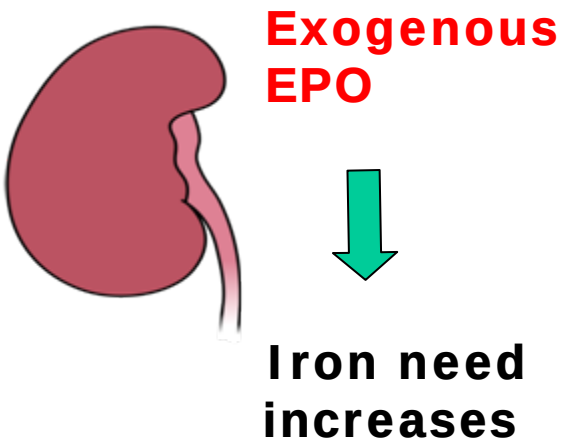
Why more iron after administration of erythropoietin ?

Normal Kidney Function



Conditions where endogenous EPO is insufficient:

- renal insufficiency
- cancer (overproduction of cytokines)



Erythropoiesis-stimulating agents should be used to target hemoglobin 11-12 g/dl in patients with chronic kidney disease *(or tumors)*. Intravenous iron may be beneficial for patients with hemoglobin less than 11 g/dl and transferrin saturation less than 25% despite elevated ferritin (500-1200 ng/ml).

Novak et al. Curr Opin Nephrol Hypertens. 2008 Nov;17(6):580-8.

What is the link between EPO and need of iron ?

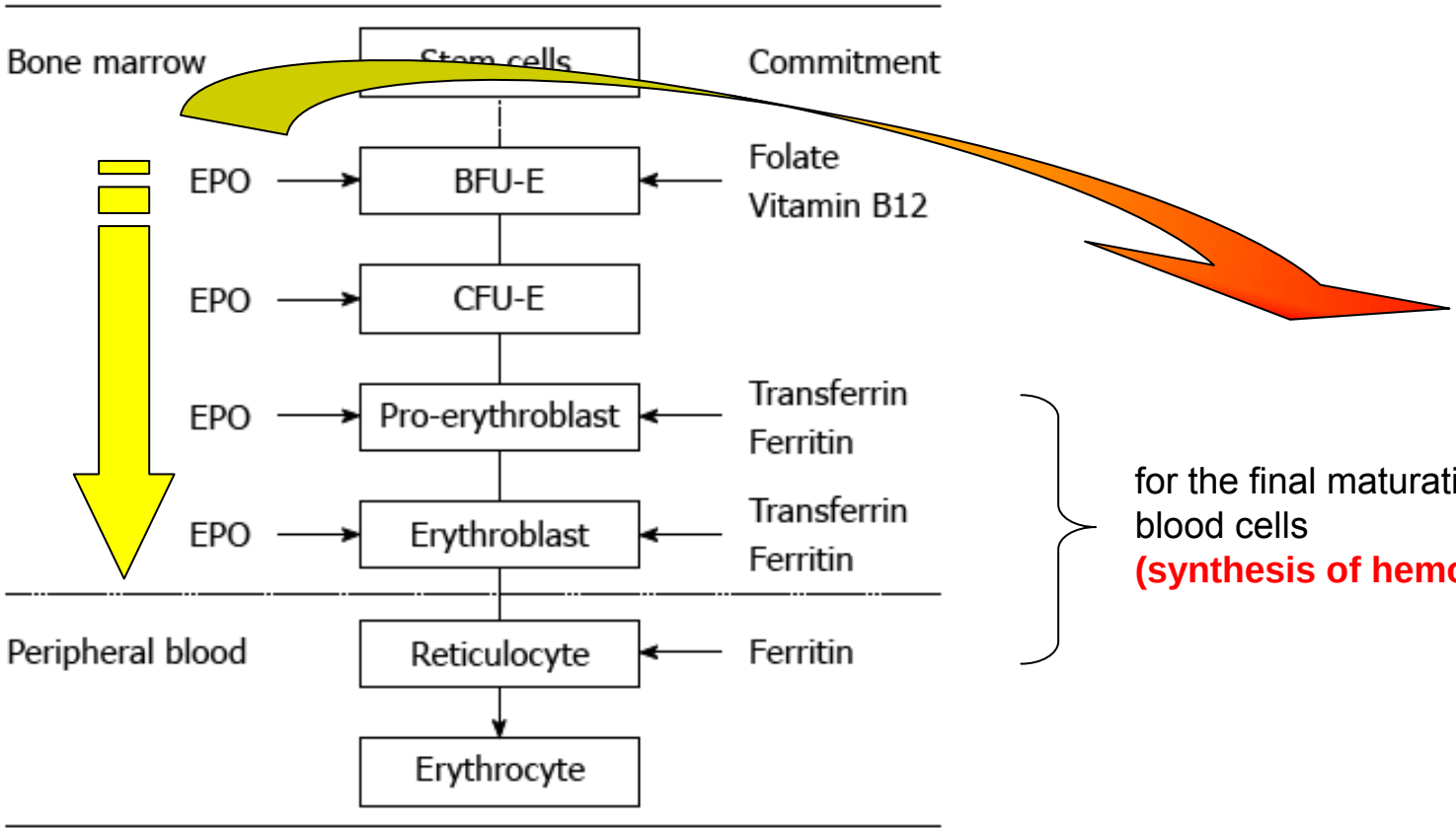


Figure 1 Major stages of human erythropoiesis showing the point of commitment, the period of EPO dependence and the requirements for essential nutrients. BFU-E: Burst-forming unit-erythroid; CFU-E: Colony-forming unit-erythroid; EPO: Erythropoietin.

Why do some patients "resist" to EPO ?

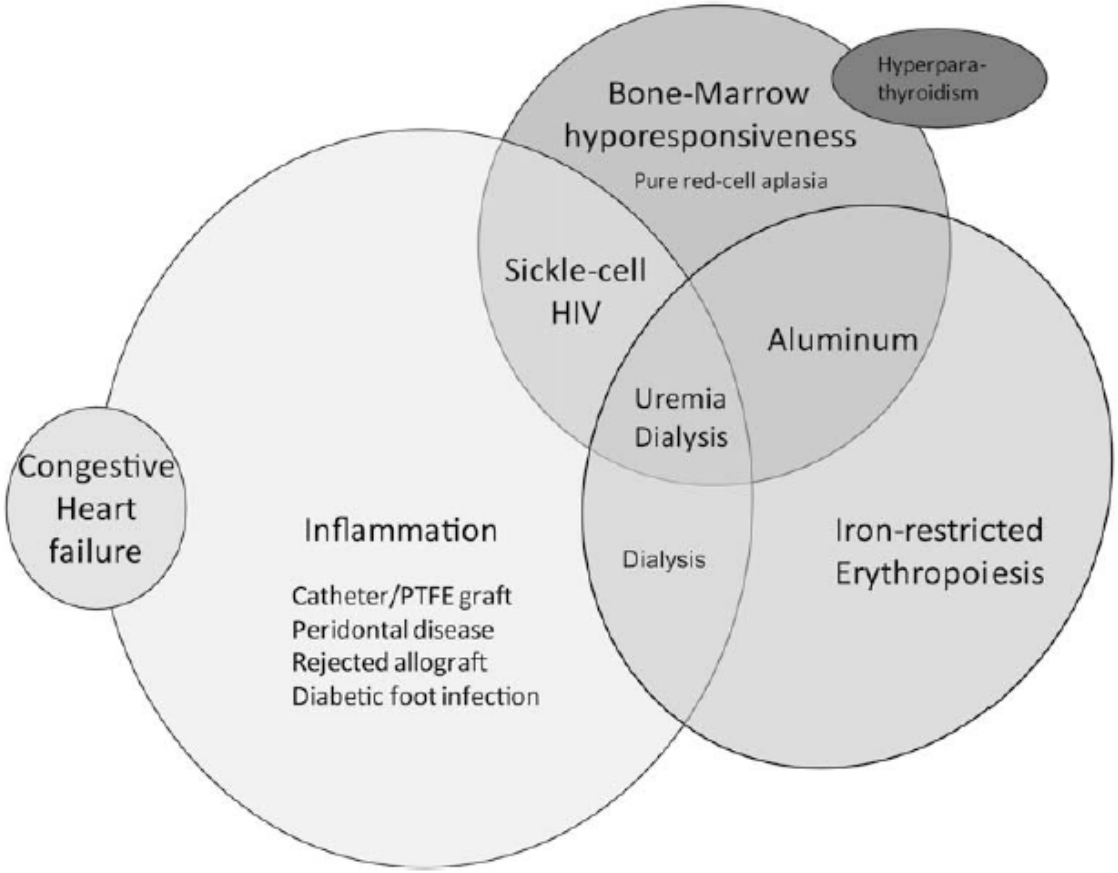


Figure 1. Causes of rHuEpo resistance: rHuEpo resistance has many causes inlcuding inflammation, iron-restricted erythropoiesis, and marrow suppression. Sometimes, various diseases and conditions share all 3 conditions. For example, patients with uremia may have blood losses, inflammation, and marrow sup pression. rHuEpo, recombinant human erythropoietin; PTFE, polytetrafluoroethylene.

Elliott et al., Advances in Chronic Kidney Disease, 2009; 16:94-100

Diagnostic and handling of EPO-resistance

Table 1. Etiology, Diagnosis, and Treatment of Erythropoietin Resistance

Cause	Findings	Intervention
Iron-restricted erythropoiesis	TSAT <20% Ferritin <1,200 ng/mL High rHuEpo dose	Maintenance IV iron
Dialysis dose	URR <65%	Improve dialysis delivery
Volume overload, congestive heart failure	Rales, peripheral edema, elevated blood pressure	Challenge dry weight Treat underlying disease
Malnutrition	Low serum albumin Micronutrient depletion	Correction of malnutrition
Access infection/Inflammation	Elevated C-reactive protein in the setting of a catheter or graft	Removal of access and transition to native fistula if possible Treat underlying disease
Hyperparathyroidism	Elevated PTH	Treat hyperparathyroidism
Aluminum intoxication	Dialysate or oral aluminum, Citrate coadministered with aluminum, hypochromic microcytic anemia	Desferrioxamine for aluminum intoxication and removal of offending agent Citrate should not be coadministered with aluminum
Dialysate contamination	Anemia in large percentage of patients at single dialysis unit	Improve dialysate water quality, ultrapure dialysate
Periodontal disease	Poor dentition, gum swelling, tenderness, and bleeding on physical examination	Referral to a dentist

TSAT, transferrin saturation; rHuEpo, recombinant human erythropoietin; URR, urea reduction ratio; PTH, parathyroid hormone.

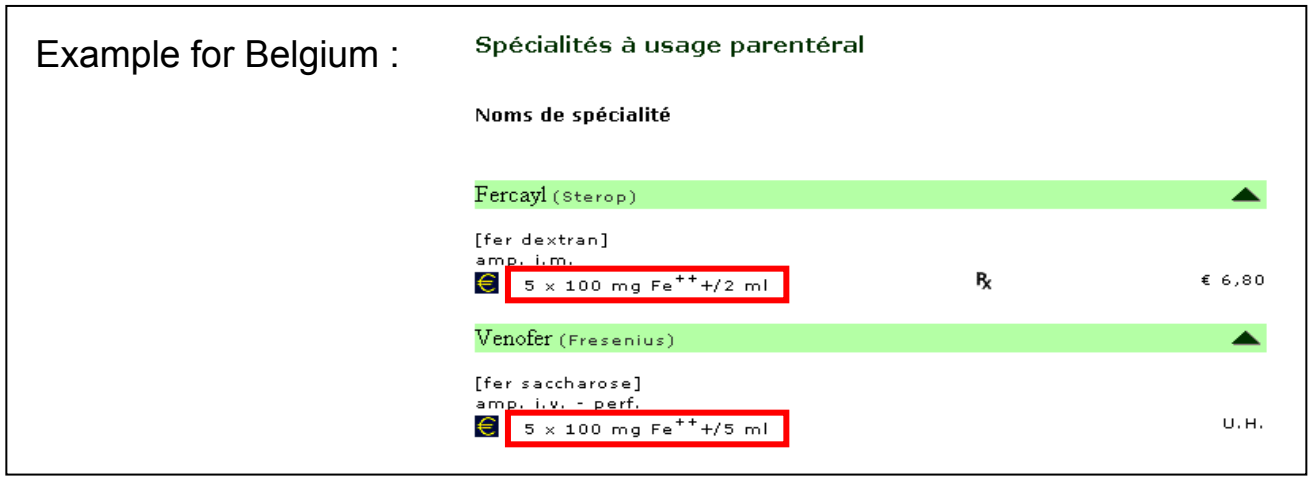
Elliott et al., Advances in Chronic Kidney Disease, 2009; 16:94-100

Can iron be administered by the parenteral route ?

A few milestones:

- the early use of iron salts has been associated with very severe side effects (J. Clin. Invest. 1932; 11: 1293-1312 – N. Engl. J. Med. 1938; 219:910-912 – Blood 1946; 1:129-142)
- IV solutions with saccharose (sucrose) were found more acceptable (Lancet 1947; i:49-51)
- Fisons introduced iron dextran in 1954, first for intramuscular (Lancet 1954; ii: 942) and later on for intravenous administration
- Several other preparations of complexed iron have since then been introduced, with large variations between countries for commercialization

Example for Belgium :



But what are (some of) the problems ?

- Complexation is often insufficiently stable leading to liberation of free, toxic ionic iron, causing oxidative stress …
  - iron gluconate (Venofer® needs to be administered by small doses (100-200 mg) over several days
- The complexing agent may cause severe adverse reactions
  - formation of anti-dextran antibodies
  - Iron-dextran needs to be administered very slowly (50 mg/min max.) and ofteh over several hoours

Warning box for Iron Dextran…

- **Anaphylactic-type reactions, including deaths**
- **Use only in those patients with iron deficiency:**
  - ✓ **Verified with lab tests**
  - ✓ **Not amenable to oral iron therapy.**
- **Resuscitation techniques and treatment of anaphylaxis and anaphylactoid shock must be readily available.**

- Most preparations do not fully take into account the way iron should be delivered to cells !

Pharmacological properties

TABLE II. Pharmacology of Parenteral Iron Products

	Iron dextran	Iron sucrose	Ferric gluconate
Bioavailability	+	++	++
$t_{½}$ elimination (hr)	6	5–6	1
Clearance (1,000-mg dose)	10–20 mg/hr[a]	Unknown	Unknown
V_d (L)[b]	Not reported	7.9	6
Dialyzed	Negligible	Negligible	Negligible
Safety profile	+	++	++
Pregnancy category[c]	C	B	B

[a]Cleared by the reticuloendothelial system.
[b]V_d (L), volume of distribution in liters.
[c]B and C denote pregnancy risk factors established by the FDA.

Silverstein & Rodgers, American Journal of Hematology 76:74–78 (2004)

Guidelines

TABLE III. Administration Guidelines for Parenteral Iron Products*

	Iron dextran	Iron sucrose	Ferric gluconate
Concentration	50 mg/mL (2-mL vial)	20 mg/mL (5-mL vial)	12.5 mg/mL (5-mL ampule)
IV injection (maximum rate)	NTE 50 mg/min	NTE 20 mg/min	NTE 12.5 mg/min
Test dose	*Required* on first infusion	Physician discretion	Physician discretion
Test dose	25-mg IV slow IV push	25-mg IV slow push	25-mg IV slow push or 25 mg in 50 mL of NS IV over 60 min
Dosing	100 mg	100 mg	125 mg
IV injection	100 mg over 2–5 min	100 mg IV over 5 min	125 mg IV over 10 min
Maintenance dose	Daily until calculated total amount required has been reached	1–3 times week	1,000 mg over 8 dialysis sessions
Minimum cumulative dose	Based on iron replacement calculations	1,000 mg	1,000 mg
Stability	Not reported	48 hr (concentration of 0.5–2 mg/mL)	Not reported
Diluent	0.9% sodium chloride	0.9% sodium chloride	0.9% sodium chloride
Total dose infusion	Yes	No	No
Infusion	Dilute dose in 250–1,000 mL of 0.9% NS infuse over 1–6 hr	100 mL 0.9% NS IV over 15 min	125 mg in 100 mL of NS IV over 1 hr
Routes	IM (INFed) IV infusion	IV injection IV infusion	IV injection IV infusion

*Abbreviations: NTE, not to exceed; NS, normal saline.

Silverstein & Rodgers, American Journal of Hematology 76:74–78 (2004)

How is iron delivered to cells ?

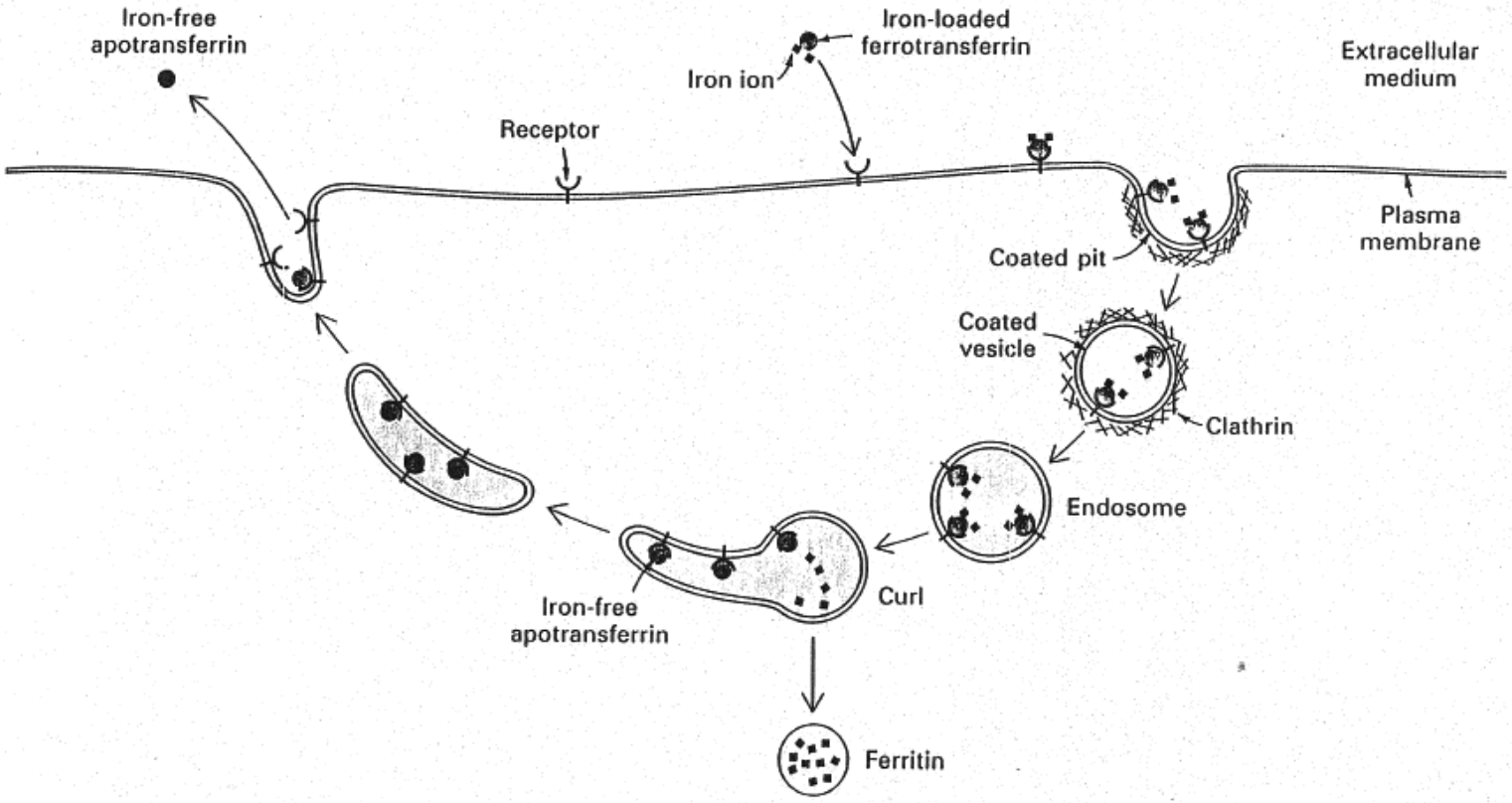
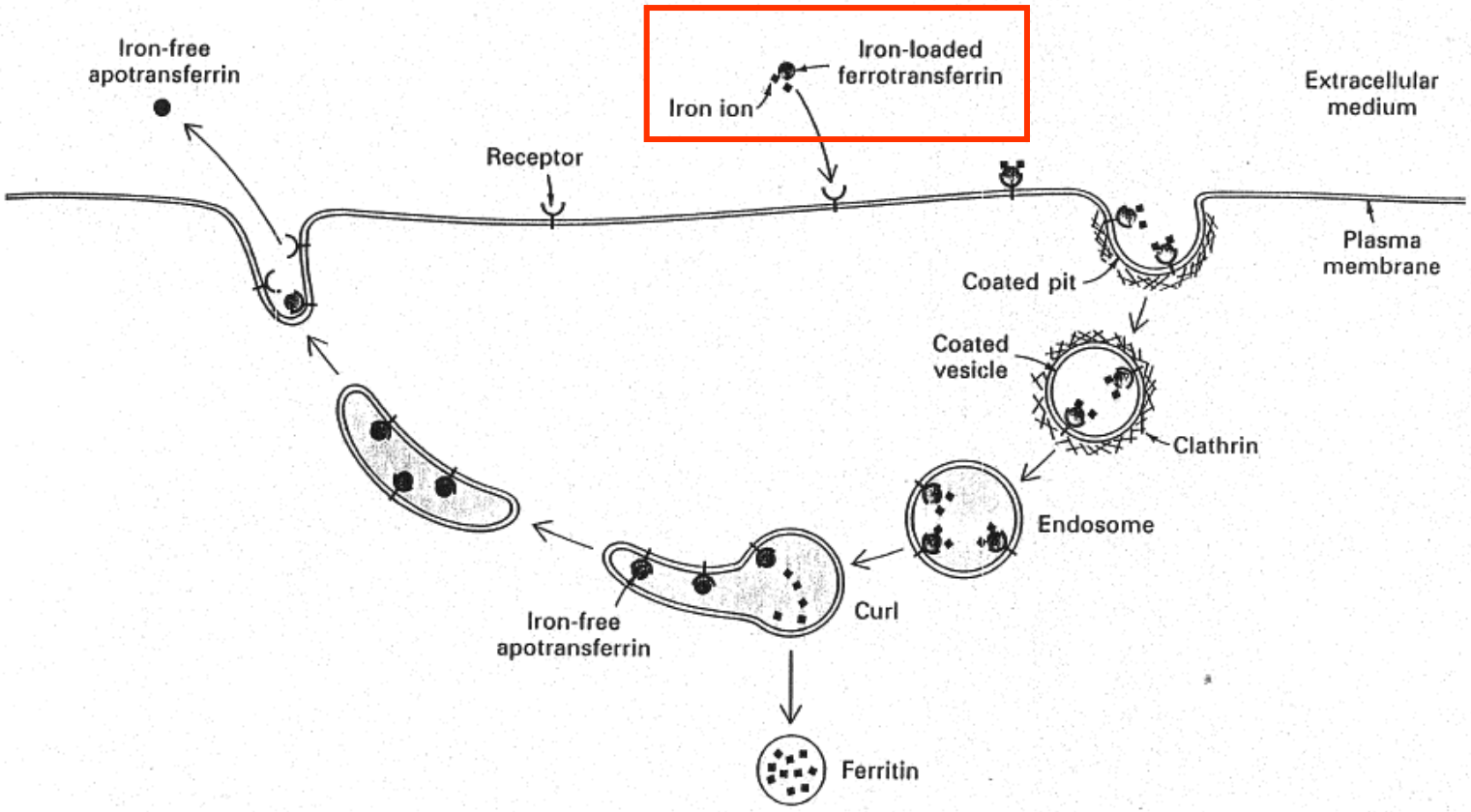


Figure 31-33
Endocytic pathway for transferrin. Iron is released in acidic endosomes. Apotransferrin and the receptor are recycled. [After A. Dautry-Varsat and H. F. Lodish. How receptors bring proteins and particles into cells. Copyright © 1984 by Scientific American, Inc. All rights reserved.]

How is iron delivered to cells ?

Iron is never free in plasma but
VERY tightly bound to transferrin as Fe^{3+}



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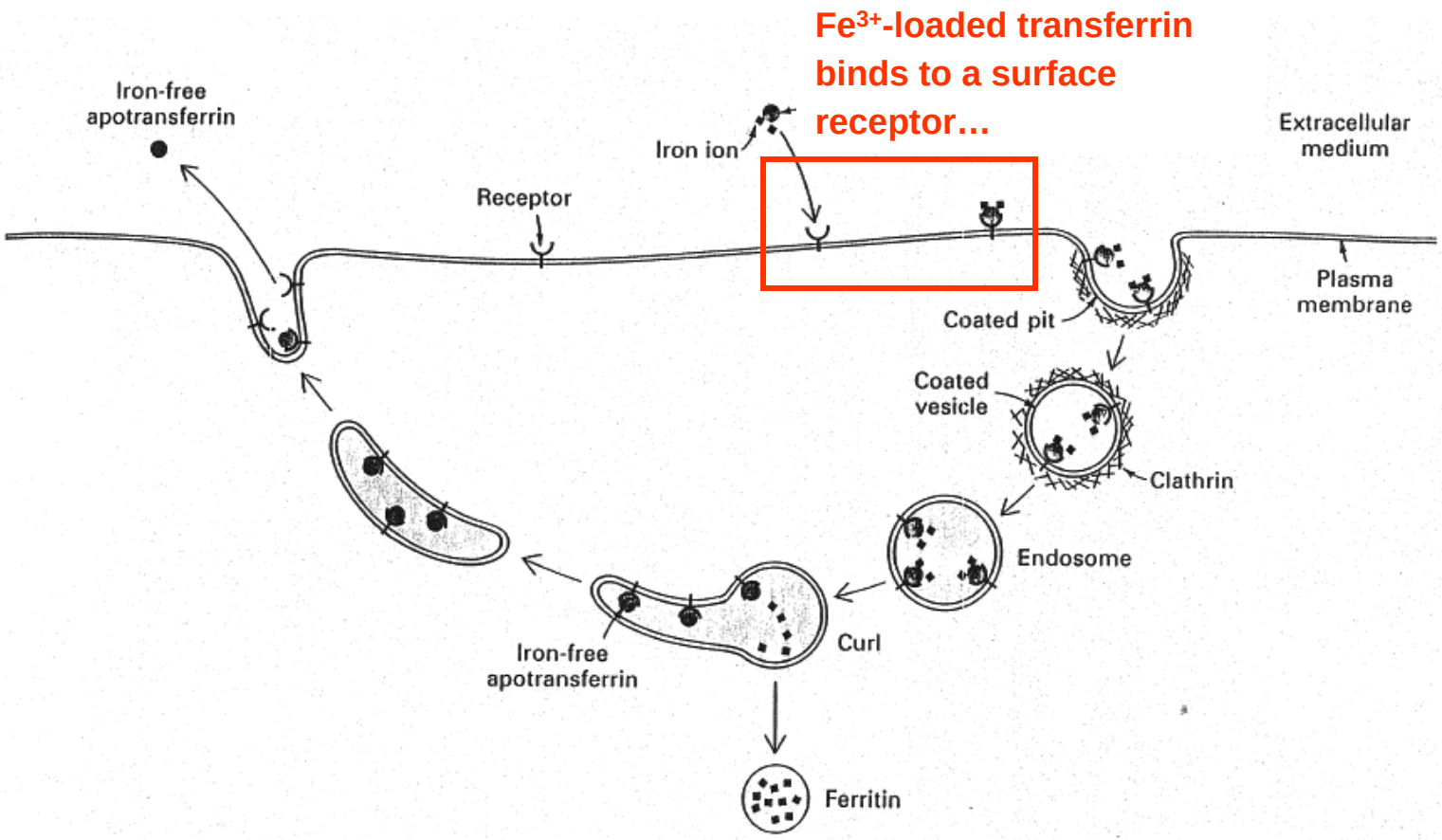
How is iron delivered to cells ?



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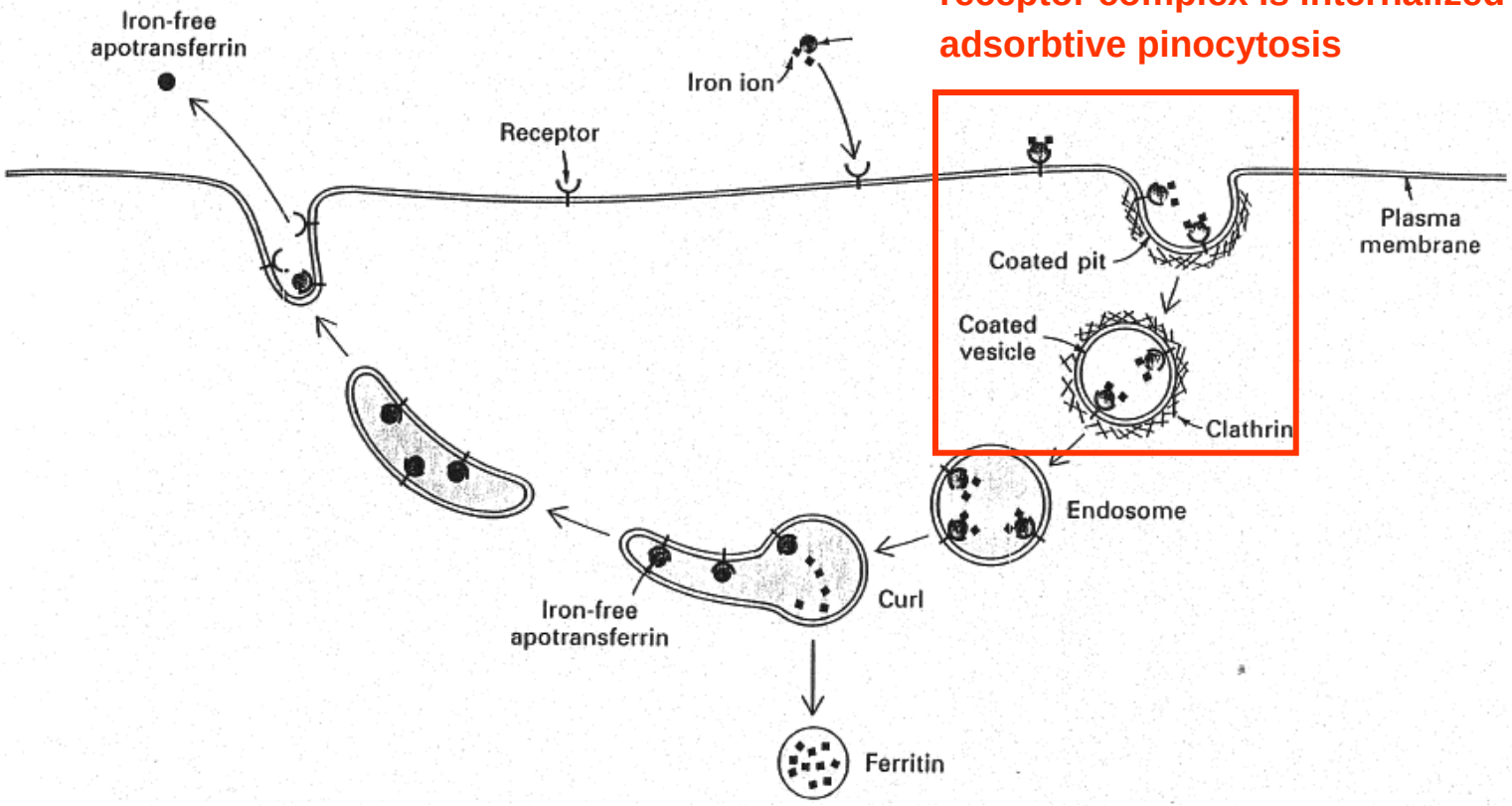
How is iron delivered to cells ?

The Fe^{3+}-loaded transferrin – receptor complex is internalized by adsorbtive pinocytosis



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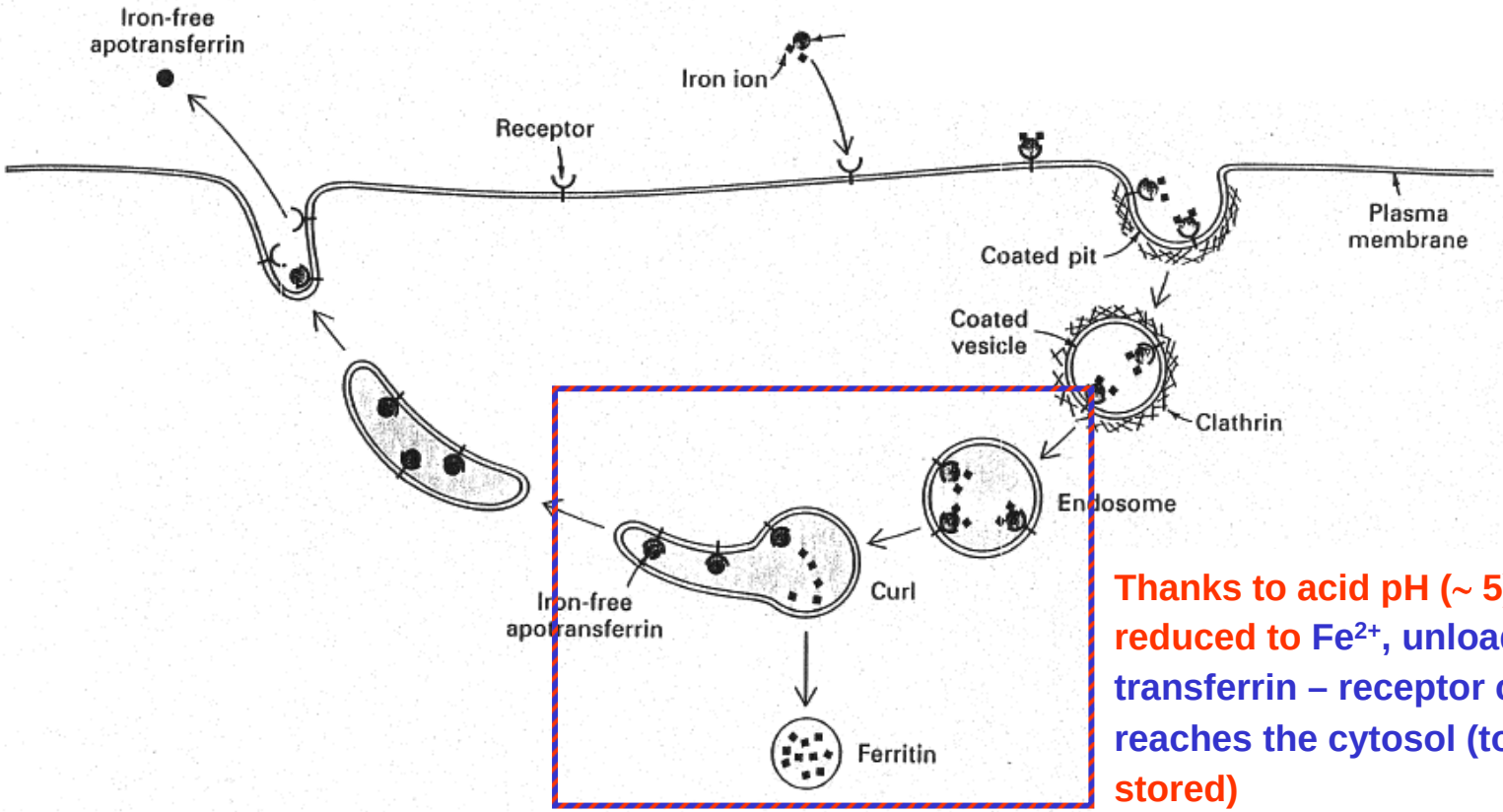
How is iron delivered to cells ?



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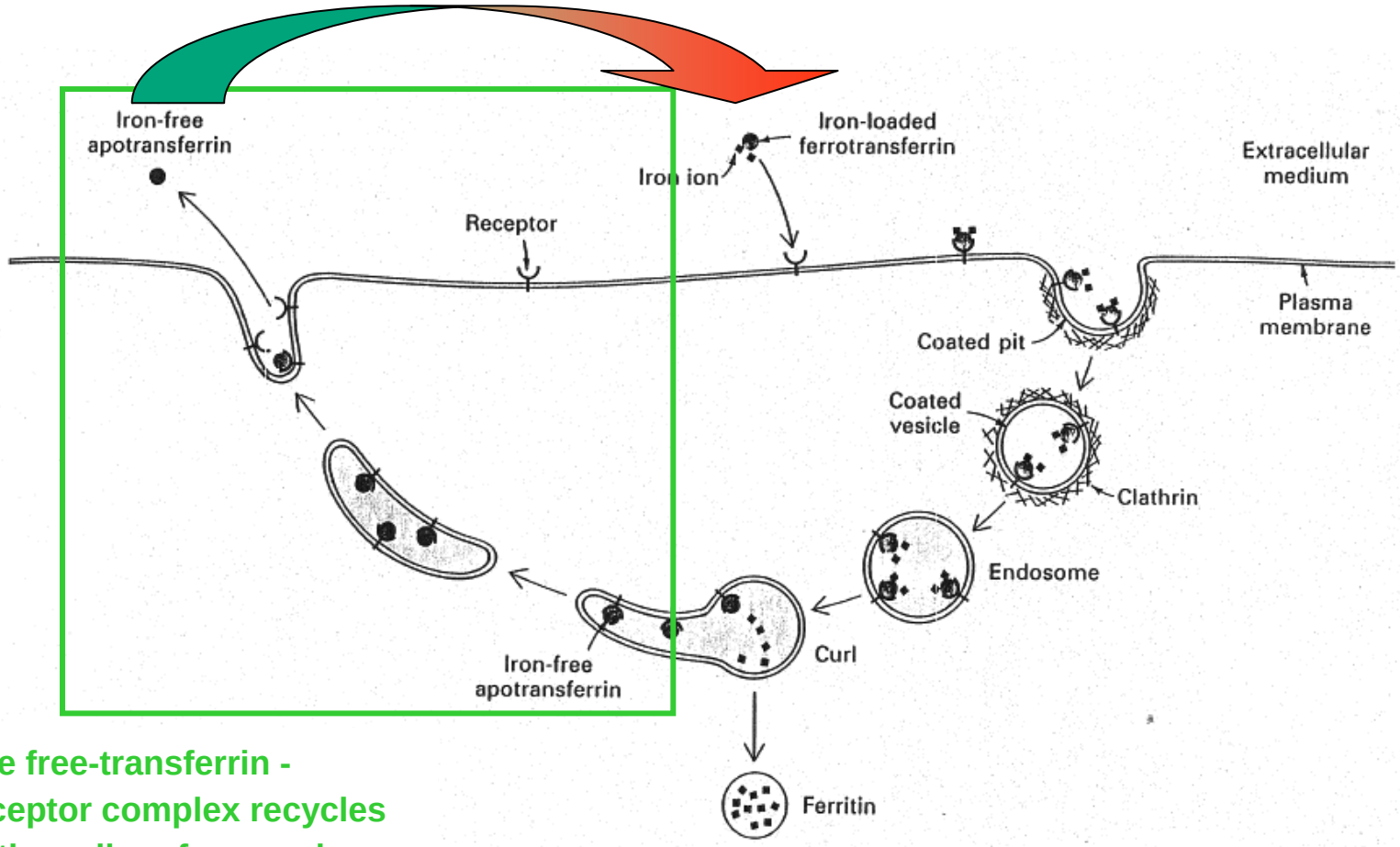
Thanks to acid pH (~ 5), Fe^{3+} is reduced to Fe^{2+}, unloaded from the transferrin – receptor complex, and reaches the cytosol (to be used or stored)

How is iron delivered to cells ?



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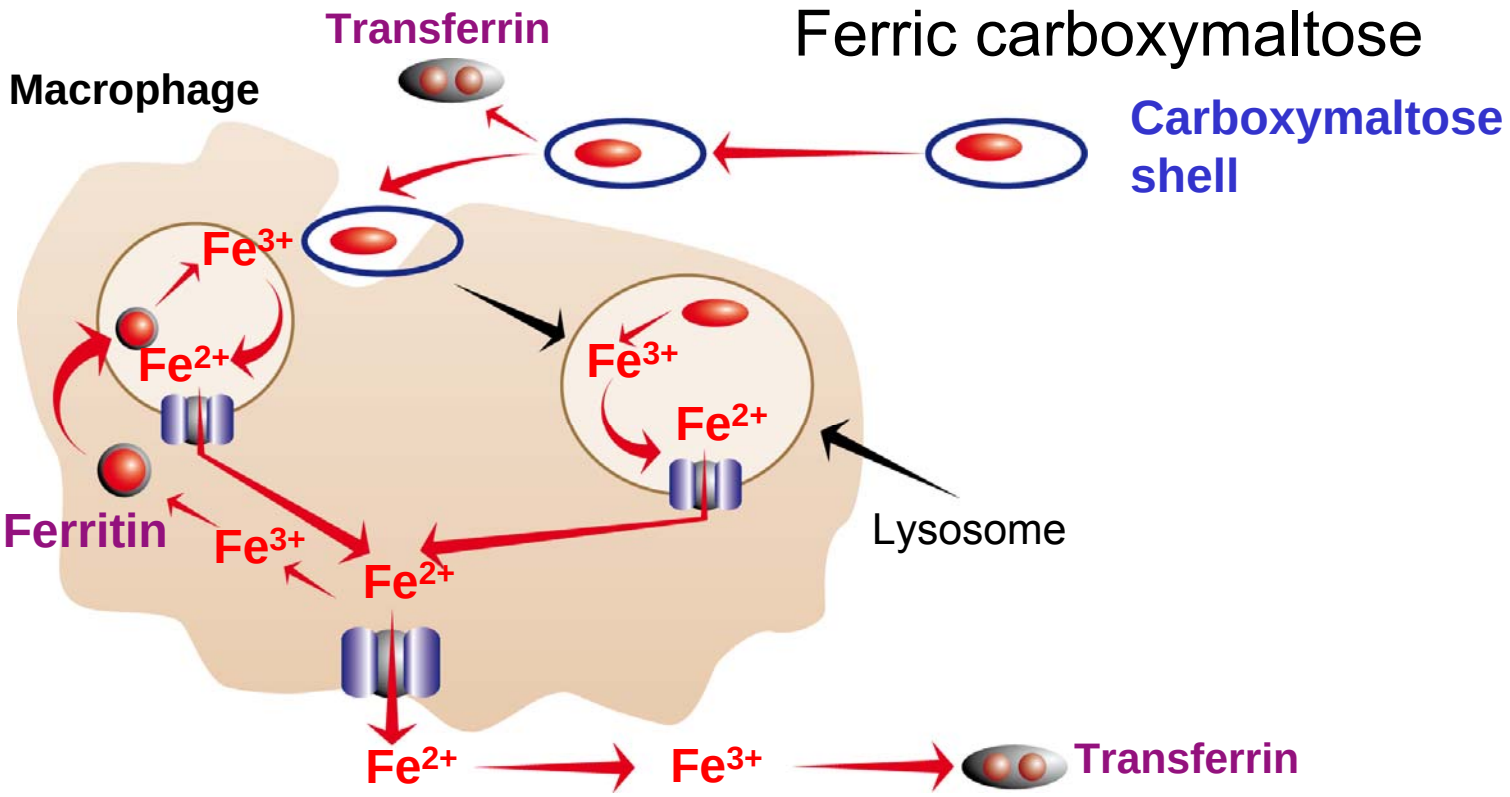
Endocytic pathway for transferrin. Iron is released in acidic endosomes. Apotransferrin and the receptor are recycled. [After A. Dautry-Varsat and H. F. Lodish. How receptors bring proteins and particles into cells. Copyright © 1984 by Scientific American, Inc. All rights reserved.]

The free-transferrin - receptor complex recycles to the cell surface… where free transferrin is liberated …

to capture any free iron and do its job again …

Why could Ferinject® be more "physiological" ?



[16] Geisser P, 1992

It mimics what transferrin would do … and it helps reloading transferrin with Fe^{3+}

Proposed use of intravenous iron in surgical patients

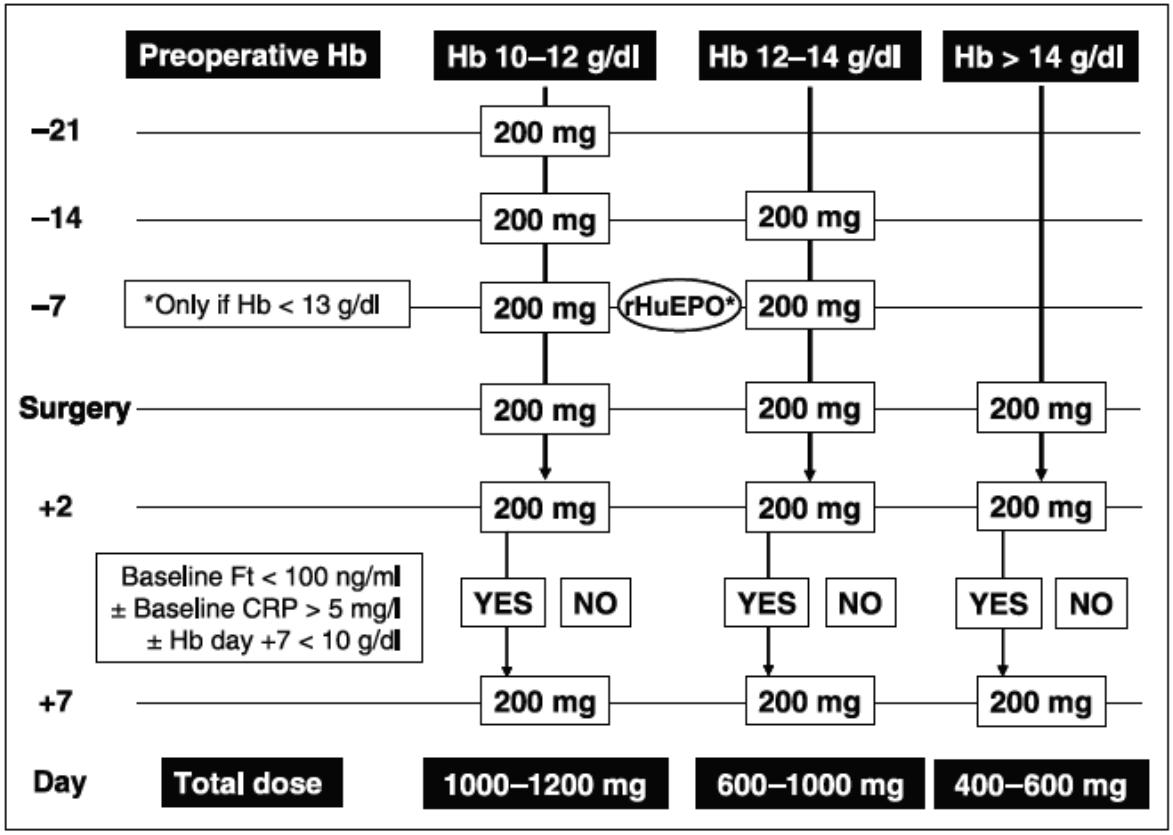


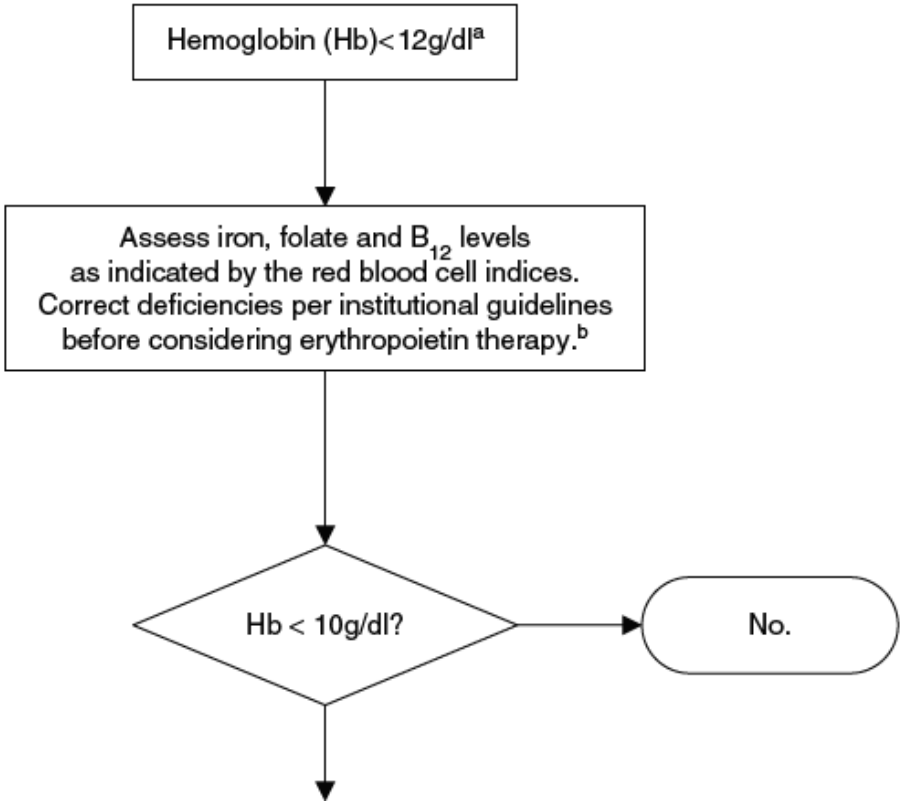
Fig. 2 A tentative algorithm for the use of intravenous iron sucrose in a 70-kg patient scheduled for major orthopaedic surgery with an expected haemoglobin drop of 4 g/dl. Total iron dose (mg), total iron deficiency (TID) + surgical iron loss (SIL); TID = [target Hb (g/dl) – actual Hb (g/dl)] × weight (kg) × 2·4; where target Hb is 14 g/dl and 2·4 is a factor (Hb iron content × blood volume × 1000); SIL = expected Hb drop (g/dl) × 165; assuming that 165 mg of iron are needed to raise Hb by 1 g/dl; day, perioperative day (–preoperative, +postoperative); Ft, ferritin; CRP, C-reactive protein.

Munoz et al. Vox Sanguinis (2008) 94: 172–183

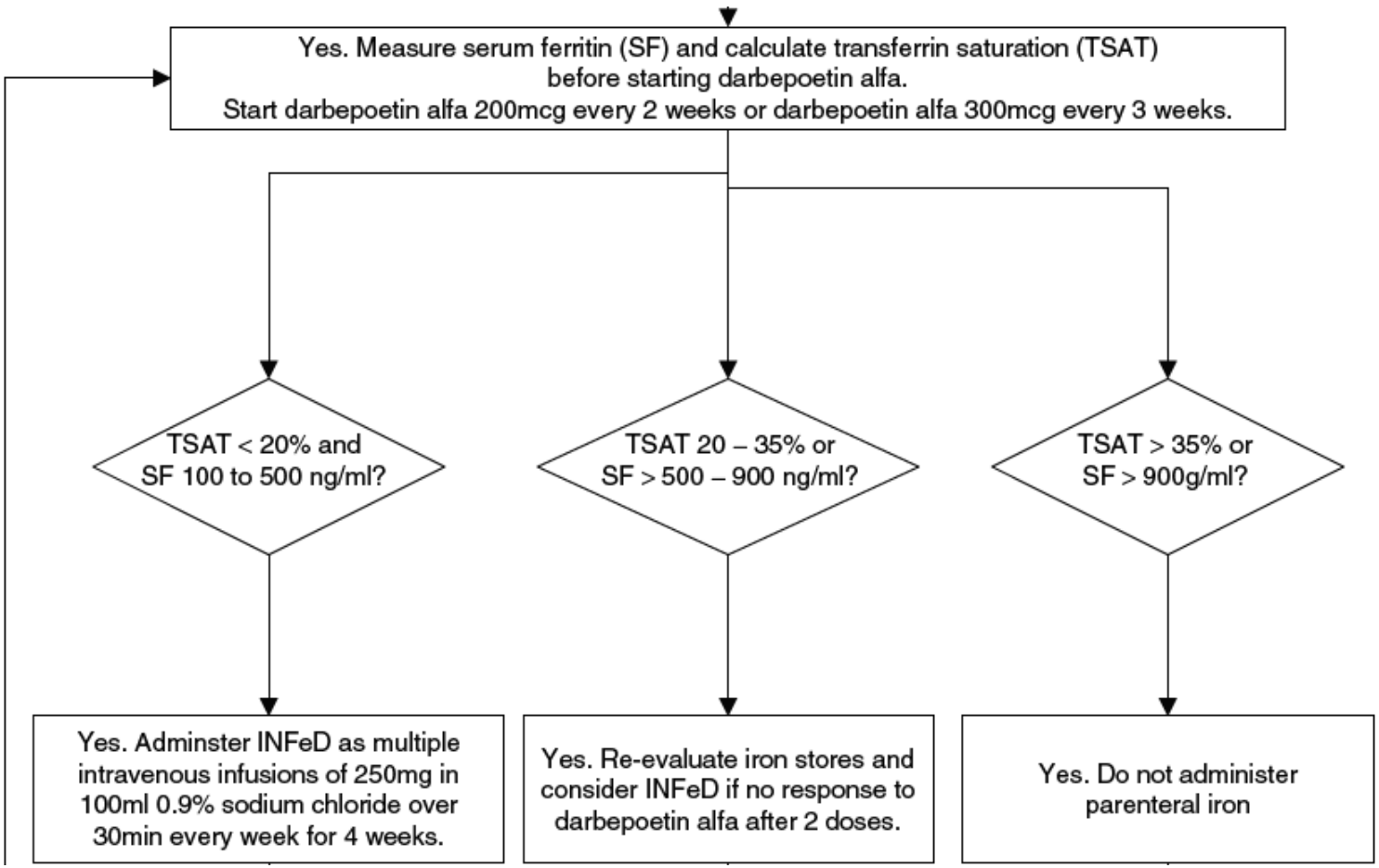
Proposed use of intravenous iron in cancer patients

Our institutional guidelines for the assessment of iron stores in patients with cancer- or treatment-related anemia and the administration of parenteral iron with ESAs in patients with non-myeloid malignancies with chemotherapy-induced anemia.

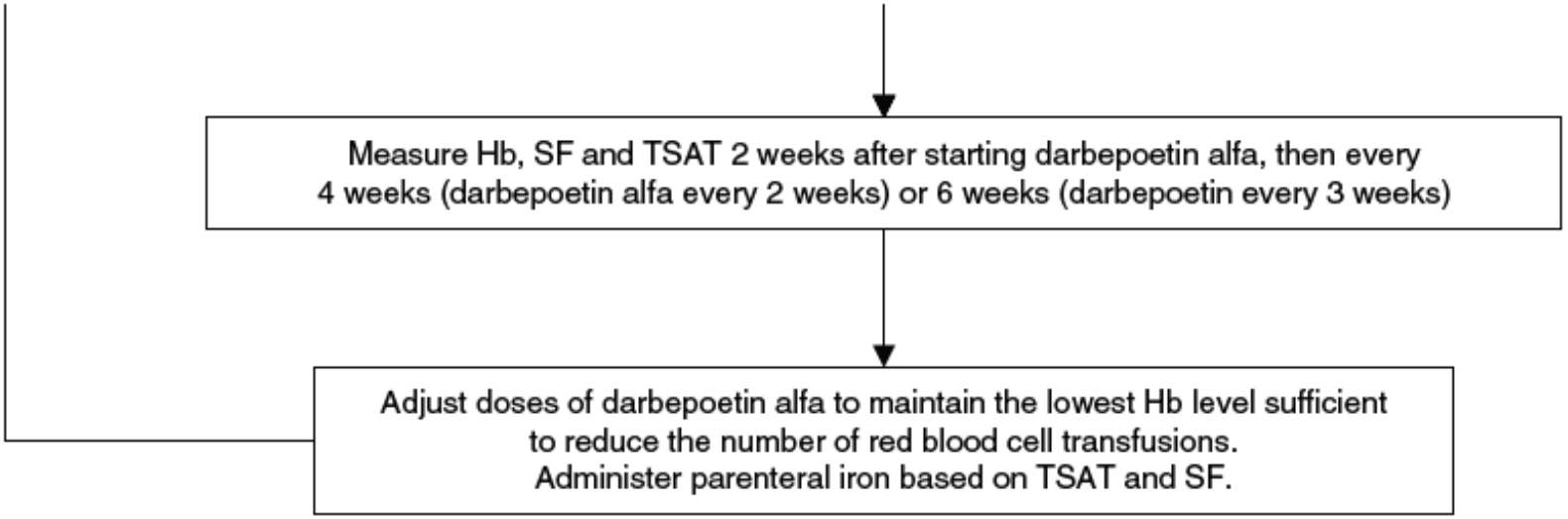
J Oncol Pharm Practice, Vol 14: No 1, 2008



Proposed use of intravenous iron in cancer patients (2 of 3)



Proposed use of intravenous iron in cancer patients (3 of 3)



[a]These guidelines are strictly to guide the adminstration of ESA therapy and patenteral iron in patients with non-myeloid malignancies currently receiving chemotherapy.
[b]Iron deficiency anemia is defined as a TSAT <20% or a serum ferritin <100 ng/ml. These guidelines are not intended to guide the adminstration of iron with this underlying diagnosis.

Is infection a risk of iron therapy ?

- This has been a **much controversial area**… with suggestions and experimental evidence that iron supplementation
  - will increase host defenses (PMN use oxydant species to kill bacteria)
  - BUT will also promote microbes' growth because they may need iron…*
- Most evidences come from studies with **oral administration** in 3d world countries with undernourished populations (probably deficient in iron) and high incidence of malaria…
- No studies of oral iron supplementation clearly show deleterious effects in non-malarious areas…
- Milk fortification reduced morbidity due to respiratory disease in two very early studies in non-malarious regions, but this was not confirmed in three later fortification studies, (decreased morbidity rates could be achieved by breast-feeding alone).
- No systematic studies report oral iron supplementation and infectious morbidity in breast-fed infants in nonmalarious regions.

Oppnenheimer S, J. Nutr. 2001; 131: 616S–635S.

* unlikely to take place with *S. aureus* et *S. pneumoniae* because there is enough Hb where they live in humans…

Does oral iron supplementation increase infections * ?

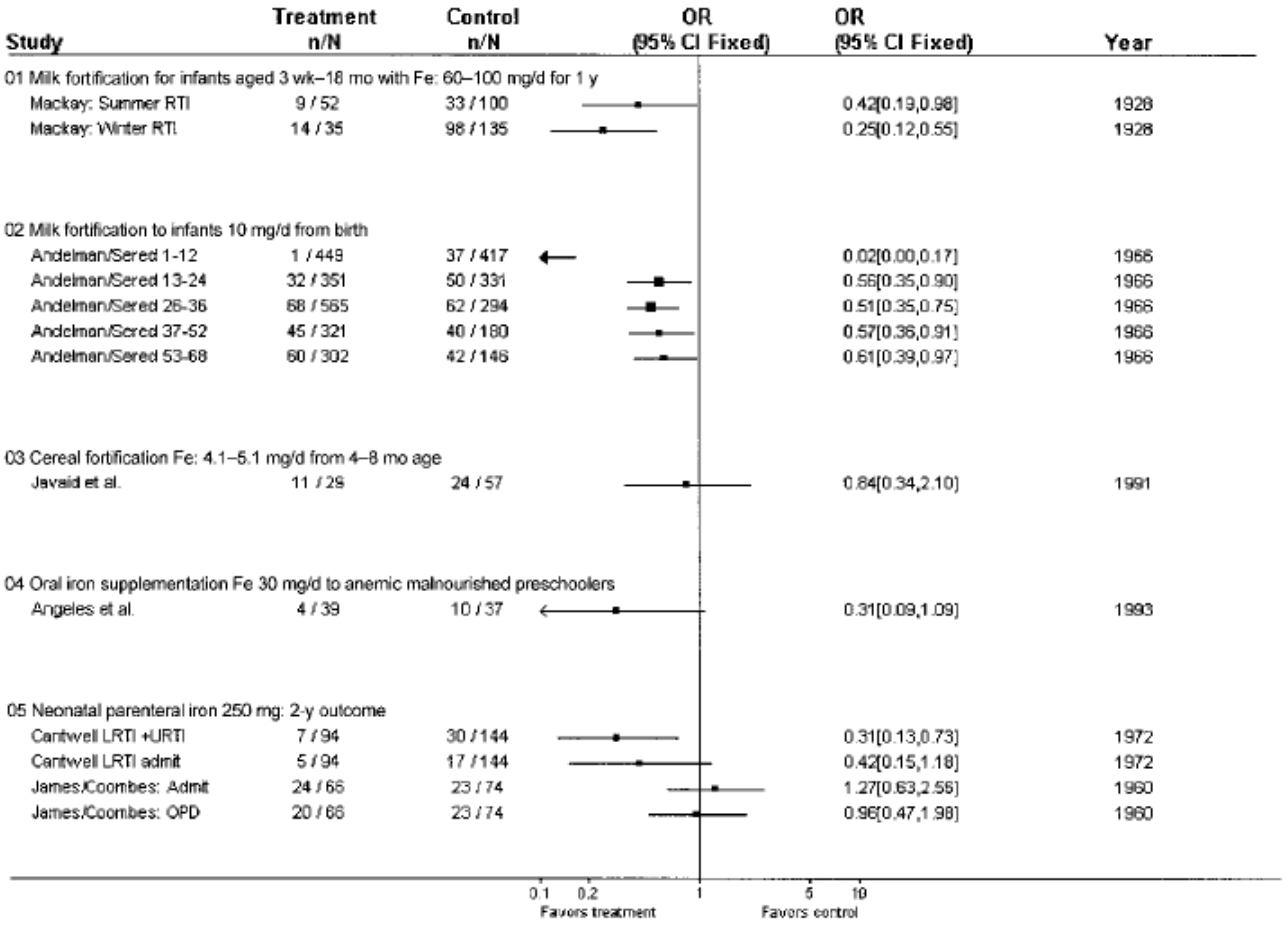


FIGURE 2 Iron trials in nonmalarious regions. Outcome: respiratory infections. Methods of administration: food fortification: infants (1–3) Andelman and Sered 1966, Javaid et al. 1991, MacKay 1928); oral supplementation: preschoolers (4: Angeles et al. 1993); parenteral: newborns (5) Cantwell 1972, James and Combes 1960). Methods of morbidity quantification: unblinded oral recall (1 and 2); field clinical assessment (3 and 4) prospective hospital based clinical assessment of serious infections (5); active case detection (1–4); prospective passive case detection (5), historical controls (1). LRTI, lower respiratory tract infection; URTI, upper respiratory tract infection; OPD, outpatient detection.

* in non-malarious areas…

Does oral iron supplementation increase infections * ?

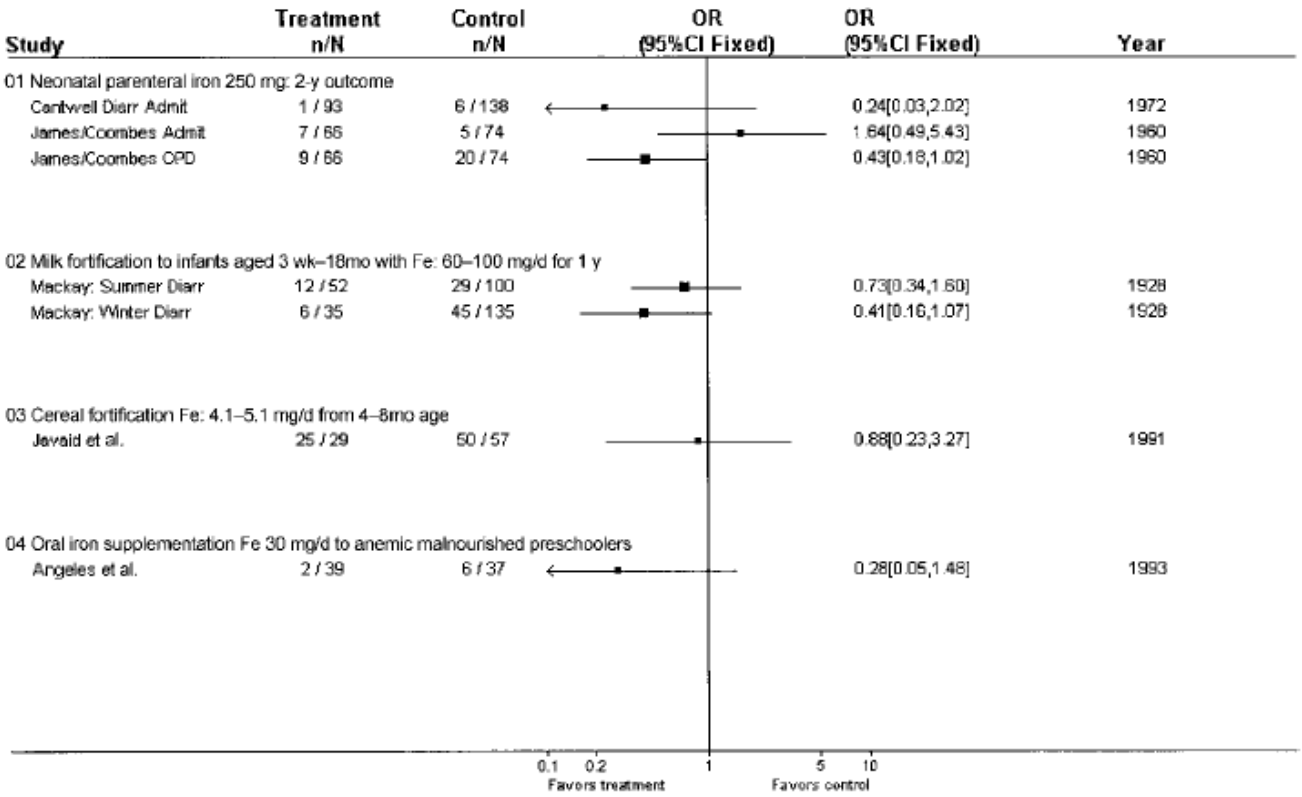


FIGURE 3 Iron trials in nonmalarious regions. Outcome: diarrheal infections (all types). method of administration: parenteral iron: infants (1: Cantwell 1972, James and Combes 1960); food fortification: infants (2: MacKay 1928 and 3: Javaid et al. 1991); oral supplementation: preschoolers (4: Angeles et al. 1993). Methods of morbidity quantification: hospital based clinical assessment of serious infections (1); unblinded oral recall with historical controls (2); field clinical assessment (3 and 4); prospective passive case detection (1); prospective active case detection (2–4). OPD, outpatient detection.

* in non-malarious areas…

What about infections in "Western" patients ?

Surg Infect (Larchmt). 2009 Feb;10(1):9-19.

Randomized, double-blind, placebo-controlled trial of effects of enteral iron supplementation on anemia and risk of infection during surgical critical illness.

Pieracci et al. Department of Surgery, Weill Cornell Medical College, New York, New York 10021, USA.

BACKGROUND: Critical illness is characterized by hypoferremia, iron-deficient erythropoiesis (IDE), and anemia.

SETTING: Enteral iron supplementation (ferrous sulfate 325 mg three times daily) or placebo until hospital discharge (97 vs. 103) in surgical patients

OUTCOMES: hematocrit, iron markers (i.e., serum concentrations of iron, ferritin, and erythrocyte zinc protoporphyrin [eZPP]), red blood cell (RBC) transfusion, transfusion rate (mL RBC/study day), nosocomial infection, antibiotic days, study length of stay (LOS), and death.

RESULTS: No difference with respect to incidence of infection (46.8% vs. 48.9%; p = 0.98), antibiotic days (14 vs. 16; p = 0.45), LOS (14 vs. 16 days; p = 0.24) or mortality rate (9.4% vs. 9.9%; p = 0.62).

CONCLUSION: Enteral iron supplementation of anemic, critically ill surgical patients does not increase the risk of infection and may benefit those with baseline IDE by decreasing the risk of RBC transfusion.

What about the infection risk for parenteral iron ?

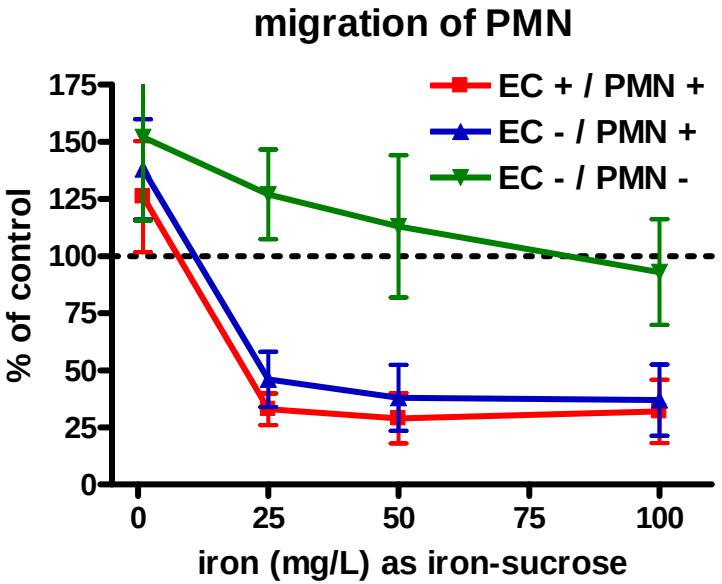
- much of the evidence is from *in vitro* studies

J Am Soc Nephrol 14: 2639–2644, 2003

Impairment of Transendothelial Leukocyte Migration by Iron Complexes

GÜRKAN SENGOELGE, JOSEF KLETZMAYR, ILSE FERRARA, AGNES PERSCHL, WALTER H. HÖRL, and GERE SUNDER-PLASSMANN

Department of Medicine III, Division of Nephrology and Dialysis, University of Vienna, Vienna, Austria



Authors' discussion: The clinical implications of our finding… are currently unknown and **require further studies.**

What you will learn in the next days about iron therapy

- Clinical studies of available formulations (as registered)
- Medical education
- Science now and in the near future
- Patient Management
- Use in Oncology (future indication ?)

- My wish list for the future of iron therapy
  - further clinical data in treatment of anemia in chronic diseases (cancer, chronic heart failure, inflammatory diseases)
  - impact of intravenous iron on (i) cytokines and inflammation-related markers in vitro and in vivo, (ii) atherotic plaques peroxidation (cardiovascular disease); (iii) infections (in vitro [comparison with iron-sucrose] and in vivo) …
  - nephrotoxicity of new formulations in comparison with iron-sucrose

Where is Louvain ?

Where we are now, in the outskirts of Brussels for the Faculty of Medicine of the French speaking Catholic University of Louvain (*Université catholique de Louvain*)

original place of the University (founded in 1425), and present place of the Flemish-speaking Catholic University of Louvain (*Katholieke Universiteit Leuven*)

Where the other Faculties of the French-speaking *Université catholique de Louvain* are located (in a place called *Louvain-la Neuve*)

And here is how it will look when you come and visit us …

the Cellular and Molecular Pharmacology team