ANEMIA OF CHRONIC DISEASE

(ACD)

seminar

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2007

VERY COMMON !!!

In hospitalized patients is the second most common after iron deficiency

OFTEN NEGLECTED !!

- **chronical infections**
- **chronical non infectious inflammations**
- **autoimmune diseases**
- **malignancies**
- **trauma, postoperative situations**

mild to moderate anemia

usually normocytic, normochromic,

later can become

hypochromic and microcytic

- accompanies infectious, inflammatory and tumorous diseases (also *anemia of inflammation*, AI)

- can develop rapidly in acute diseases

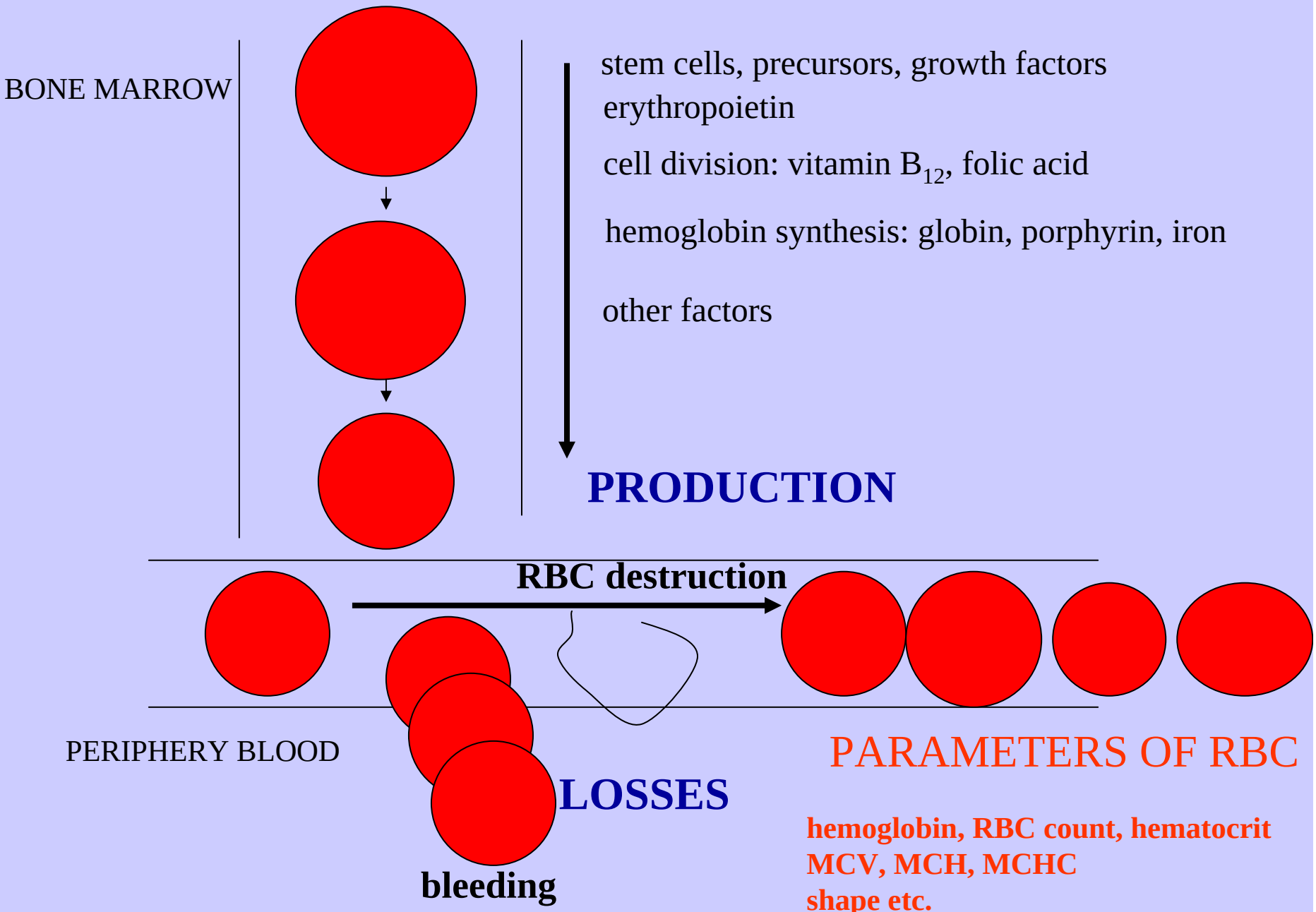
Sequelae:

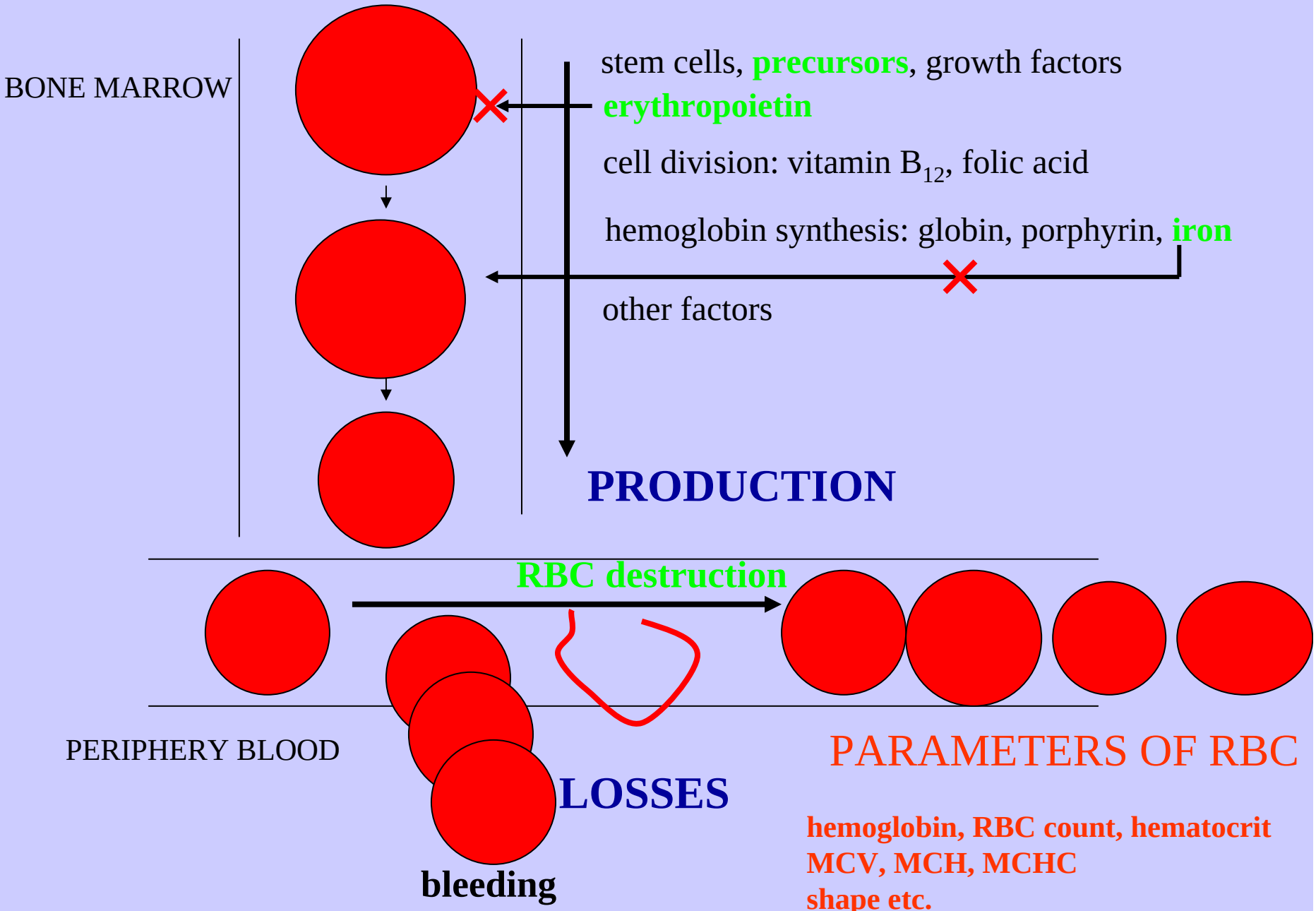
-general sequelae of anemia

-in severe diseases it further deteriorates clinical course, quality of life and sometimes even the survival rate

General ethiopathogenesis of anemias

- Anemias are caused by insufficient **production** or by increased **losses** of RBC
- Both can be caused by many factors and often combine
- **Pathogenesis of ACD cannot be explained by only one category but are combined**


BONE MARROW
stem cells, precursors, growth factors
erythropoietin
cell division: vitamin B_{12}, folic acid
hemoglobin synthesis: globin, porphyrin, iron
other factors
PRODUCTION
RBC destruction
PERIPHERY BLOOD
LOSSES
bleeding
PARAMETERS OF RBC
hemoglobin, RBC count, hematocrit
MCV, MCH, MCHC
shape etc.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Pathogenesis

immune driven (inflammatory cytokines (IL-1β, TNFα, IFNγ)

- **mildy decrease of RBC survival probably due to activation of macrophage system**
- **impaired erythropoiesis**
- **blunted erythropoietin response**
- **specific iron deficiency for erythropoiesis: iron restricted erythropoiesis**

- **supporting influence of the disease (bleeding incl. blood tests, lack of nutrition, vitamins…)**

Dysregulation of iron homeostasis

-relative iron deficiency for erythropoiesis (low iron concentration)

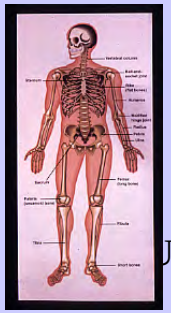
-retention of iron in reticuloendothelial system

-later real iron deficiency can develop due to decreased iron absorption

IRON

Iron is the 4th most abundant element of the Earth crust

Used by all living organisms



The man has about 4 gr of iron to 70 000 gr of body mass

Iron

Part of heme/non-heme proteins
Important functions:

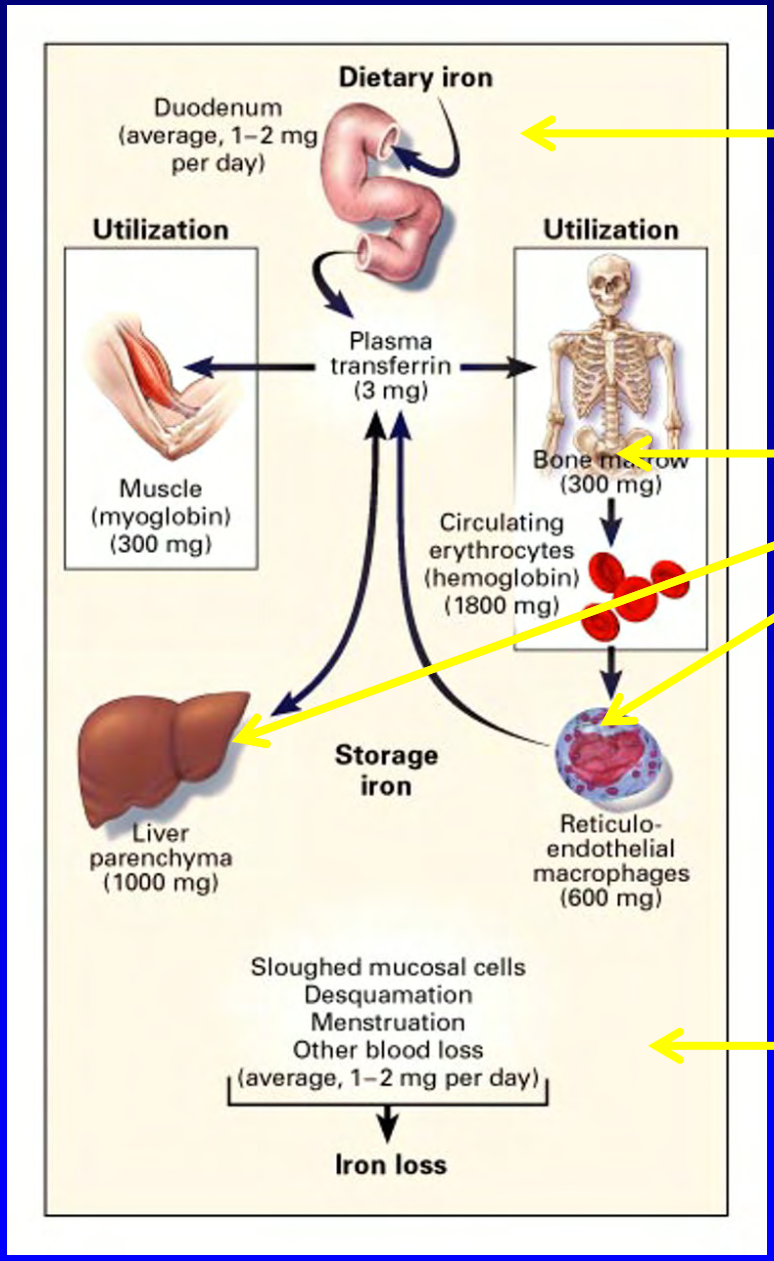
Energy formation
*** oxygen transport (hemoglobin)**
*** electrone transport (cytochroms)**
Transformation and detoxicication (cyt. P450)
Cell and tissue proliferation
Immunity

The same properties of iron utility make iron potentially

toxic element

Fenton reaction:

$$Fe^{2+} + H_2O_2 \Rightarrow Fe^{3+} + OH^{*} + OH^{-}$$



absorption 1-2 mg/den

distribution

20-25 mg/den

- utilization

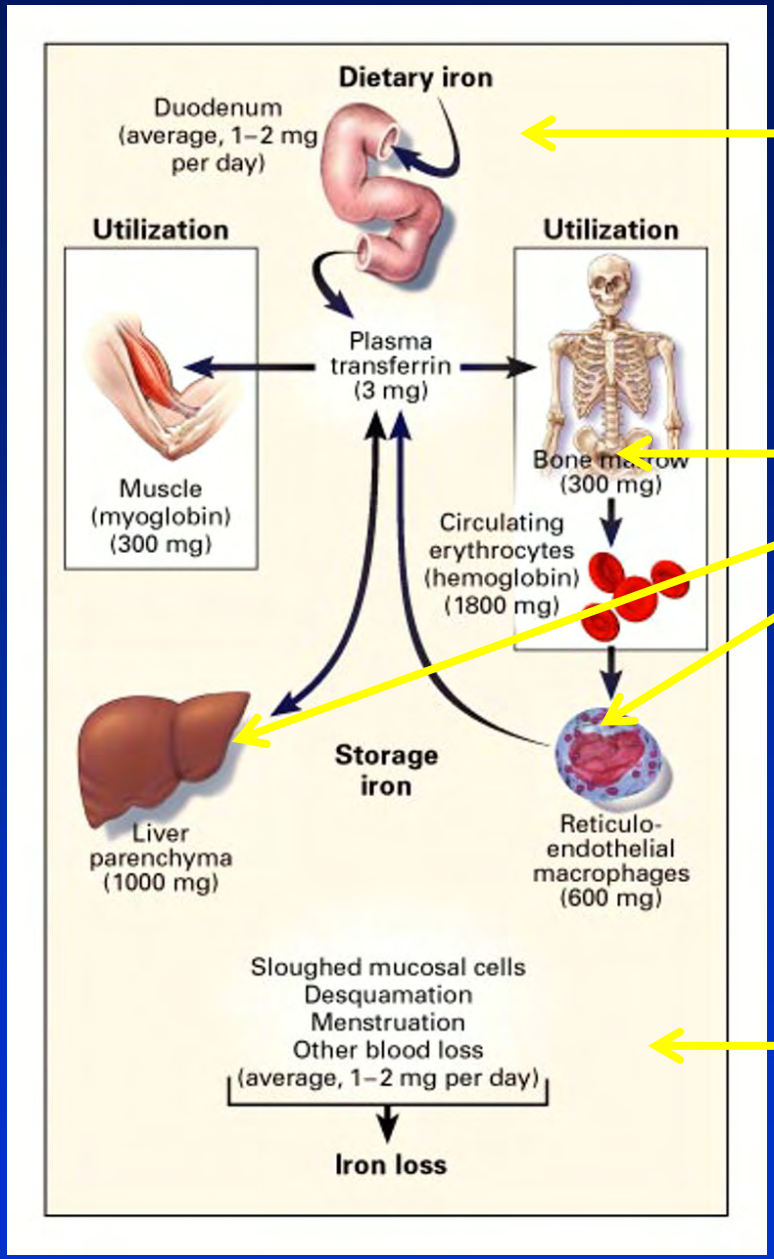
recyclation

- stores

losses 1-2 mg/den

Total amount of iron in the organism is 3000-4000 mg

Andrews, N. C. N Engl J Med 1999;341:1986-1995



absorption

REGULATION

distribution

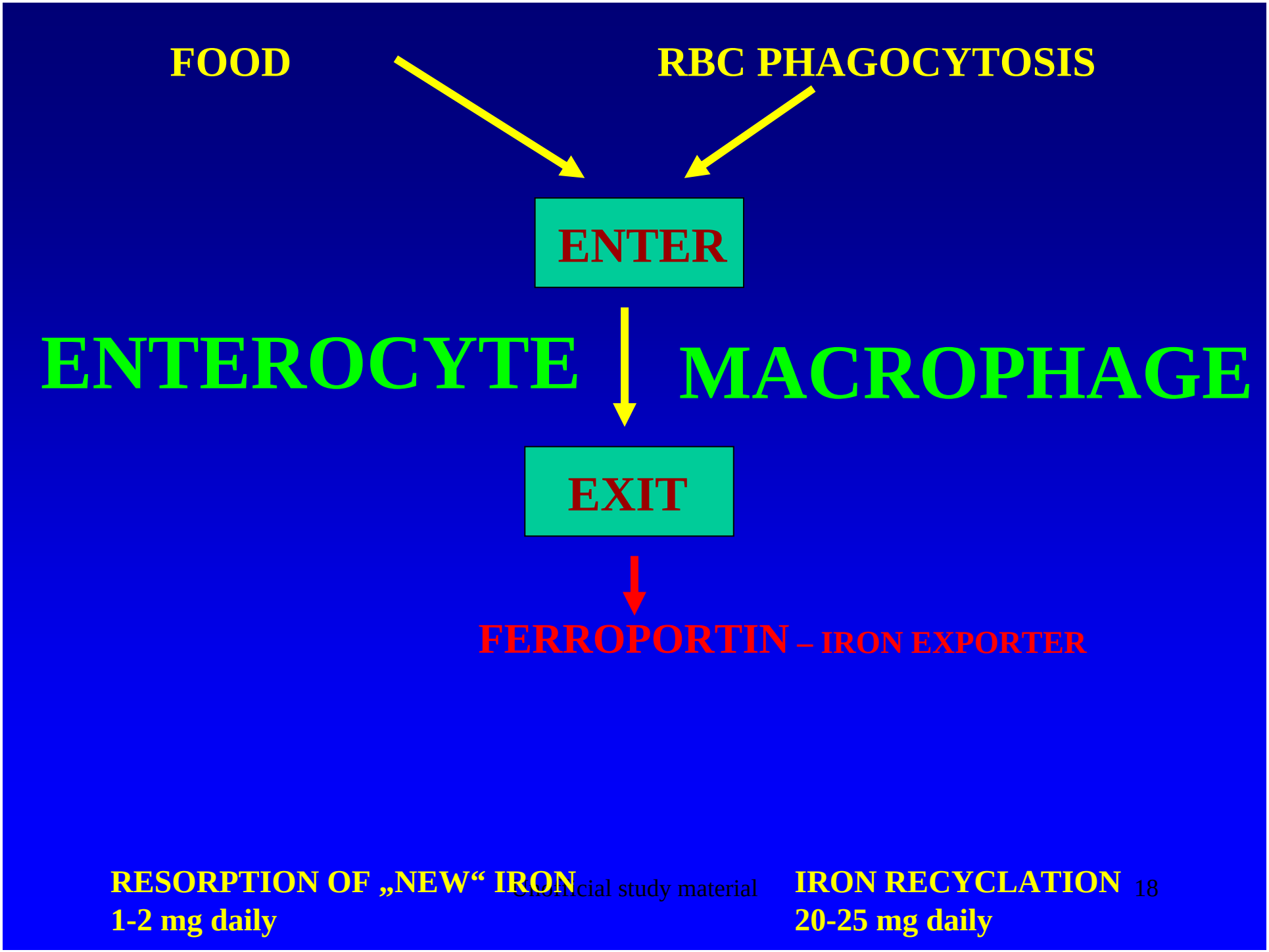
- utilization

recyclation

- stores

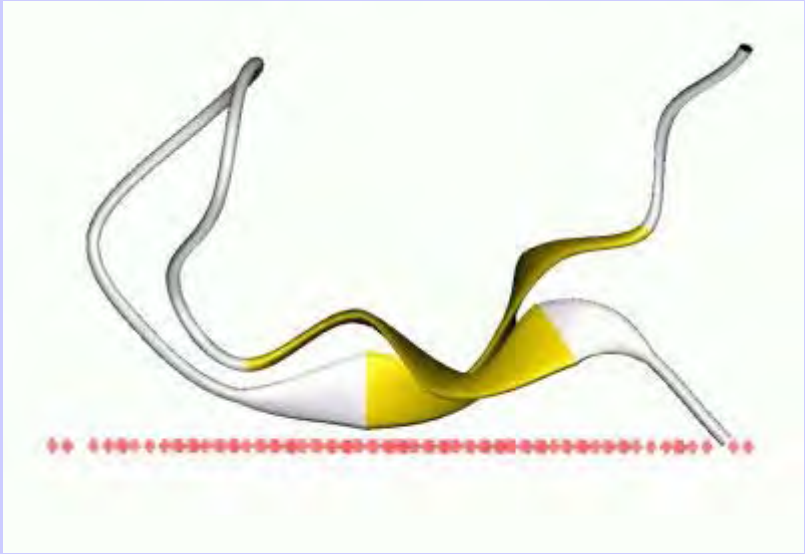
loss

Andrews, N. C. N Engl J Med 1999;341:1986-1995


FOOD
RBC PHAGOCYTOSIS
ENTER
ENTEROCYTE
MACROPHAGE
EXIT
FERROPORTIN – IRON EXPORTER
RESORPTION OF „NEW“ IRON
1-2 mg daily
IRON RECYCLATION
20-25 mg daily

What controls iron metabolism?

- HEPCIDIN



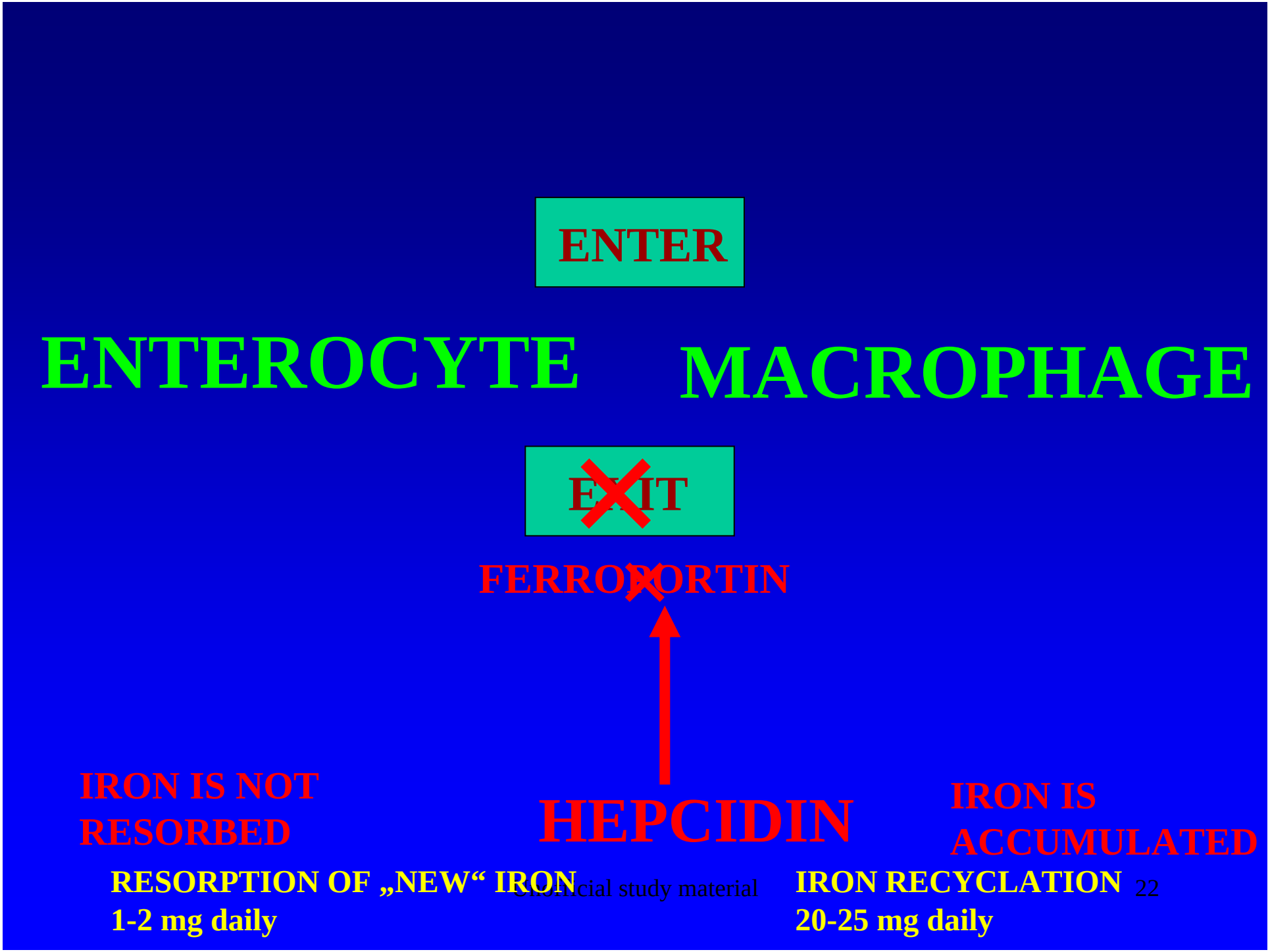
Hepcidin

(HAMP = hepatic antimicrobial peptide)

* 25-amino-acid peptide with
  4 cystine bridges
* produced in the liver (hepatocytes)
* antimicrobial action

Regulation of iron metabolism:

- decreases iron absorption by enterocytes
- causes iron sequestration in macrophages


ENTER
ENTEROCYTE
MACROPHAGE
EXIT
FERROPORTIN
IRON IS NOT RESORBED
HEPCIDIN
IRON IS ACCUMULATED
RESORPTION OF „NEW“ IRON
1-2 mg daily
IRON RECYCLATION
20-25 mg daily

Hepcidin effects

- (Fast) decrease of iron serum concentration
- Iron is accumulated in macrophages
- Iron resorption decreases
- Long-term regulation of iron amount in the body

Hepcidin disturbances

- **TOO LITTLE – excessive iron resorption**
- **TOO MUCH – insufficient iron resorption and its accumulation in macrophages**

Hepcidin regulation

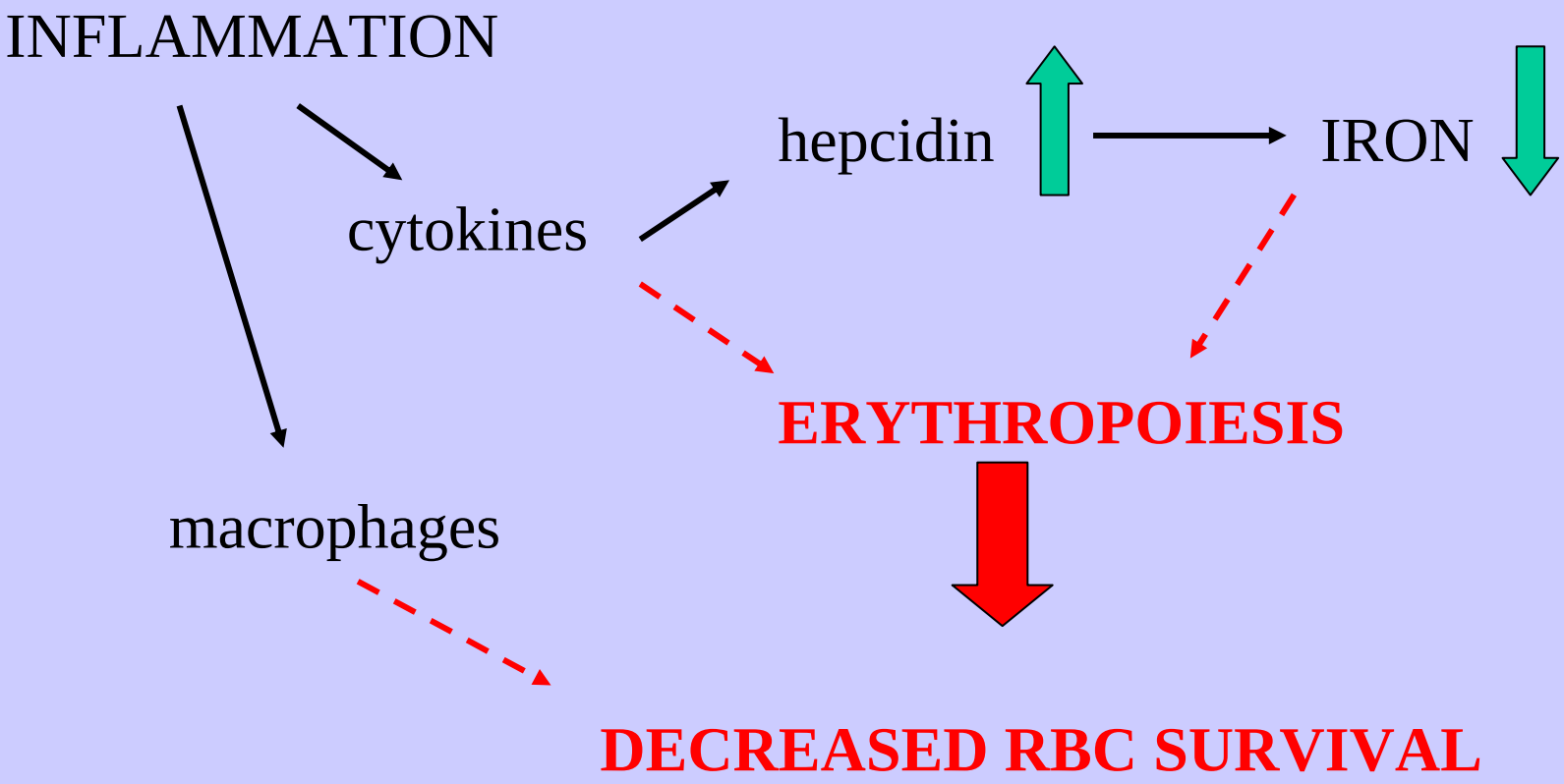
- **IRON**
  Feedback mechanism: much iron decreases further absorption

- **INFLAMMATION (cytokines – IL-6)**
  Inflammation increases hepcidin production and interferes with iron metabolism

HEPCIDIN
IS PROBABLY REGULATORY
HORMONE
OF IRON METABOLISM
IN THE ORGANISM

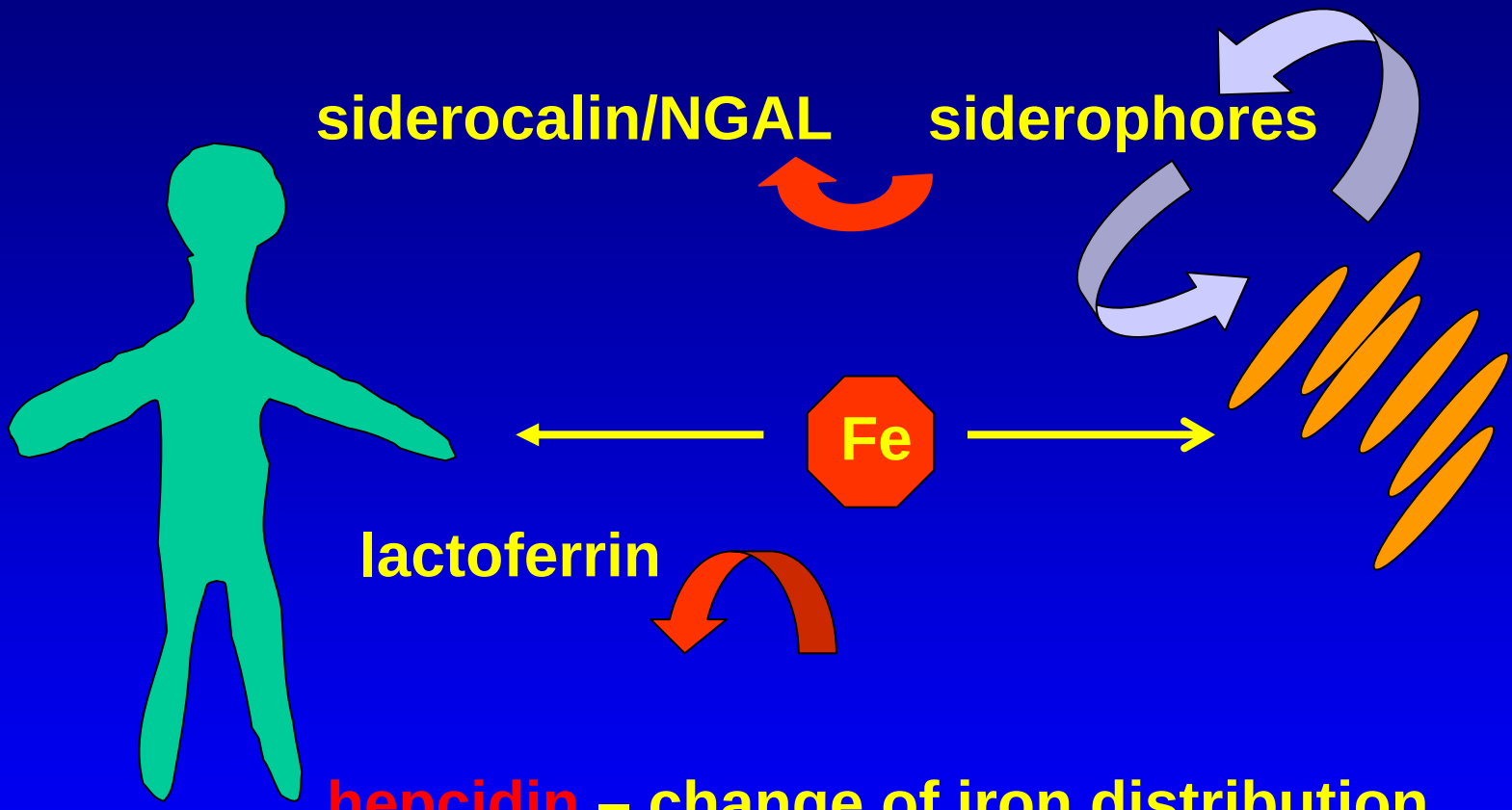
AND IT IS AS WELL
ACUTE PHASE REACTANT

Inflammation and erythropoiesis



IRON AND INFECTIONS

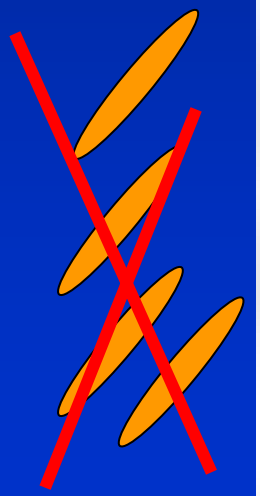
1. Necessary for bacterias
2. Necessary for immunity
    * killing bacterias (oxygen radicals)
    * mucosa and skin integrity
    * proliferation of immunity cells

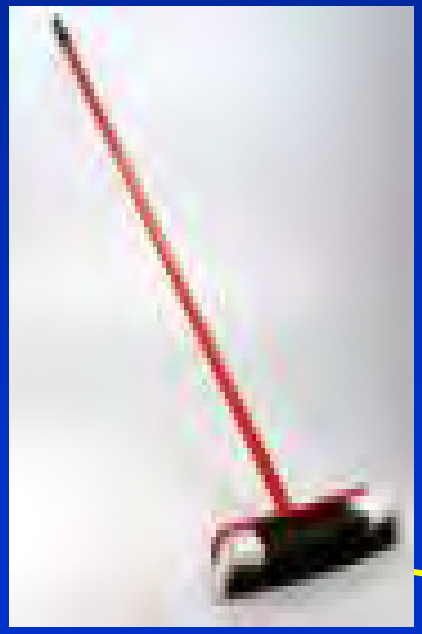


hepcidin – change of iron distribution
(decrease of resorption, MΦ sequestration)

Hepcidin

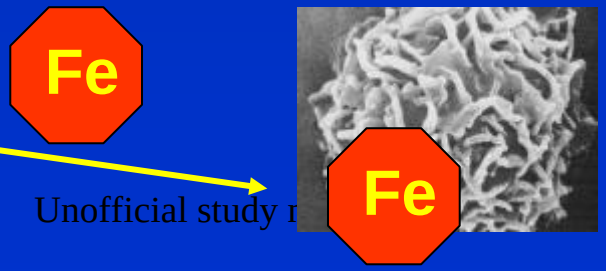
It is supposed to play a role in ACD pathogenesis, mainly in changes in iron kinetics in this anemia





relat. iron deficiency for RBC

„sweeps“ iron from bacterias

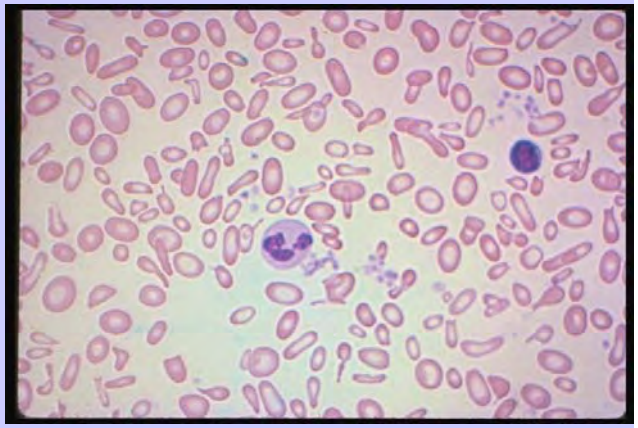


Diagnosis of ACD

- Anemia (mainly normo-, event. microcytic)
- Inflammatory disease, cancer
- Low serum iron concentration

This could be true also for **iron deficiency anemia**

- **FERRITIN** – increased
- **TRANSFERRIN** – decreases
- **IRON STORES** – sufficient



	ACD	Fe Defic
Serum Fe	↓	↓
Transferrin	N ↓	↑
% Saturation	↓	↓
Ferritin	N ↑	↓
BM Fe Stores	↑	↓

HEPCIDIN ↑ ↓

(not available in clinical practice)

Conclusions

- **Iron** is vital element which could be toxic
- Thus it must be **regulated** on local and systemic level
- Systemic regulator is peptide **HEPCIDIN**
- Iron plays important role in **inflammatory processes and infections**
- It is crucial for pathogen elimination but it is as well important for their growth and metabolism
- **Microorganisms** and human organism have mechanisms how to acquire iron
- Defence-oriented iron sequestration may contribute to the pathogenesis of **anemia of chronic disease**
- This anemia is frequent and accompanies many inflammatory, infectious and tumorous diseases
- It must be **differentiated** from real iron deficiency anemia

THE END