Centre de Référence des
Surcharges en Fer
Rares d'origine Génétique

CHU Rennes

Métabolisme du Fer

Collège de Biochimie

Paris

29 janvier 2015

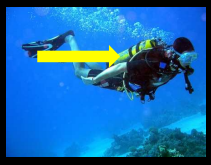
Aspects physiologiques

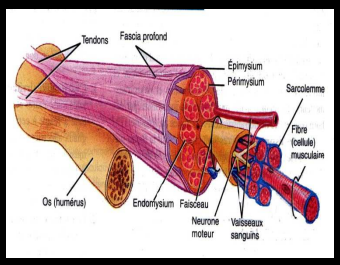
Aspects physio-pathologiques

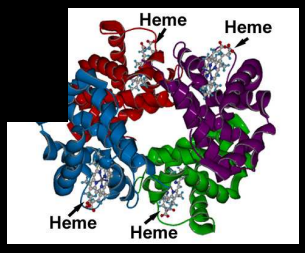
Les 10 « commandements » du fer

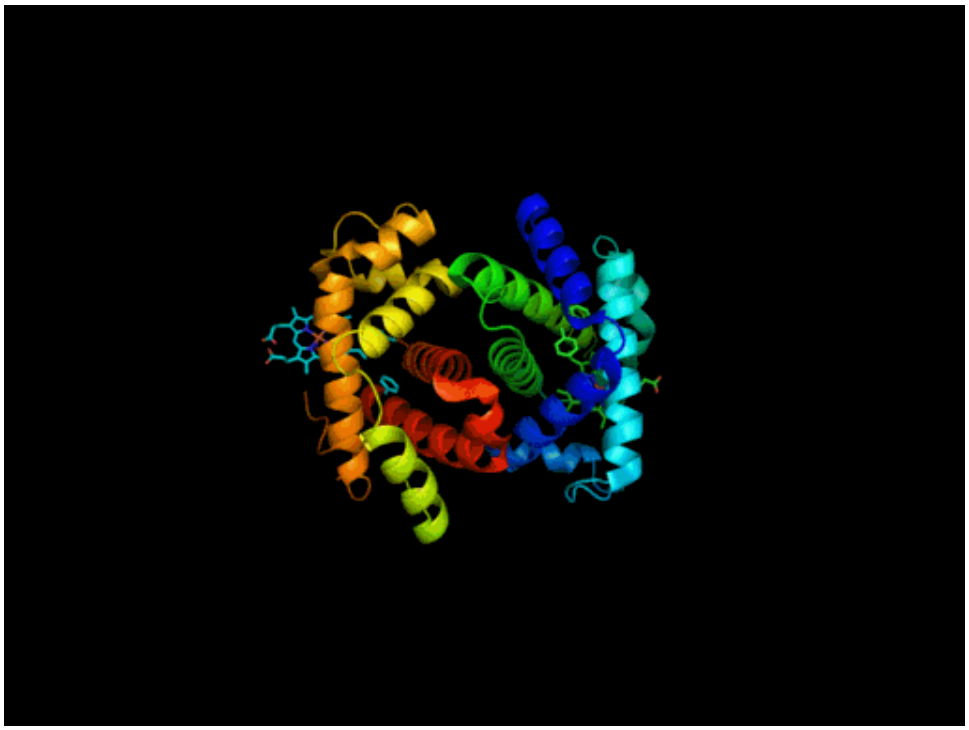
1. Le fer est indispensable

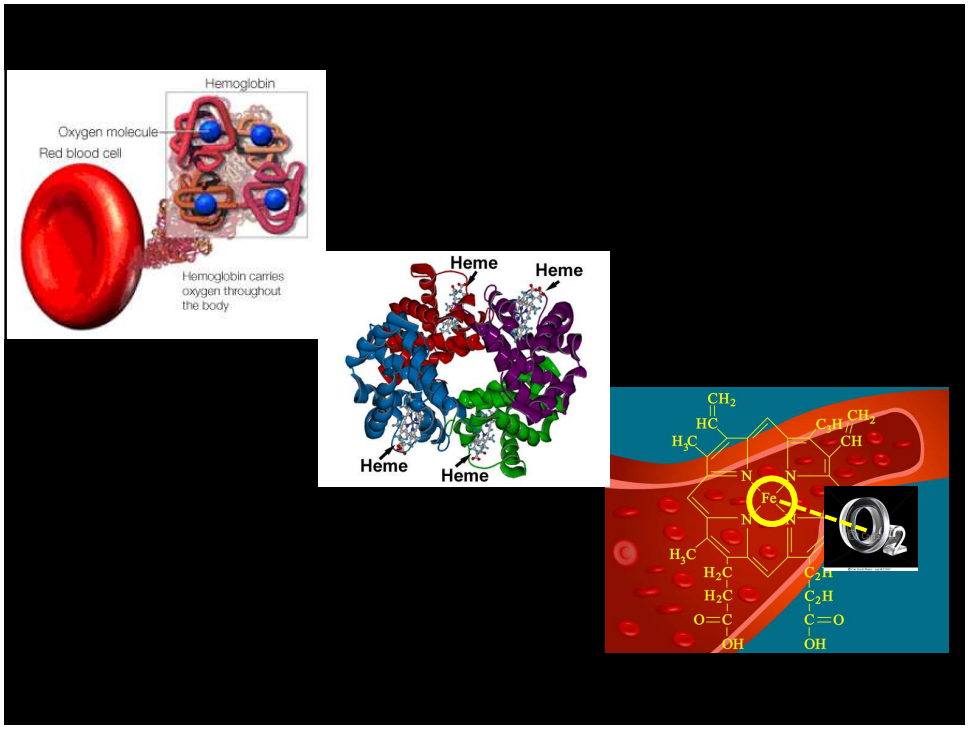
Transport de l'oxygène



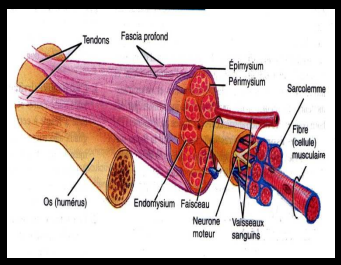







Hemoglobin
Oxygen molecule
Red blood cell
Hemoglobin carries oxygen throughout the body
Heme
Heme
Heme
Heme
CH2
HC
H3C
C2H
CH2
CH
N
N
N
N
Fe
O2
H3C
H2C
H2C
O=C
OH
C2H
C2H
C=O
OH

Transport de l'oxygène



Co-facteur de nombreuses réactions enzymatiques:

. Biotransformation des xénobiotiques

. Synthèse du collagène

. Synthèse de l'ADN…

2. L'organisme humain ne fabrique pas de fer

La seule source : alimentaire

10-20 mg/jour

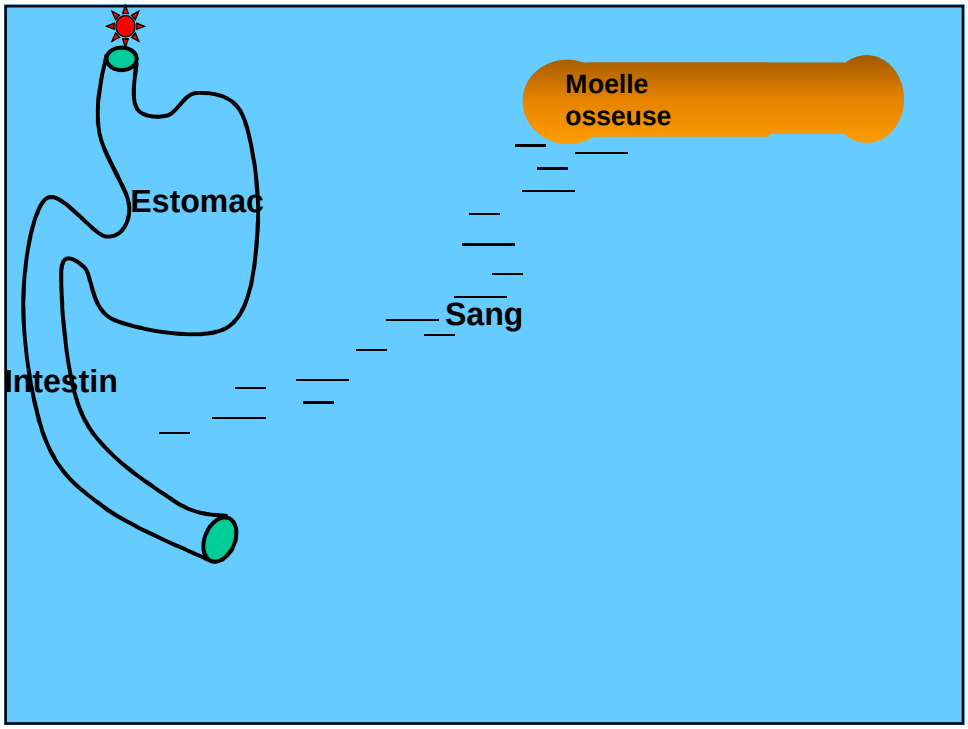
Fer héminique / Fer non héminique

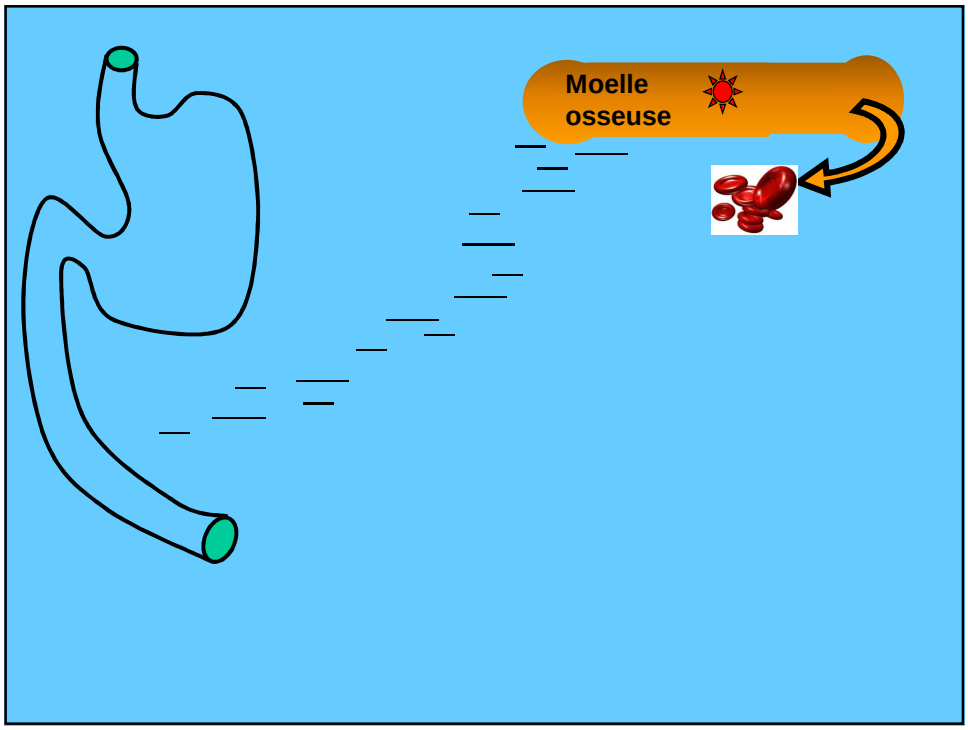
1-2mg absorbés/jour

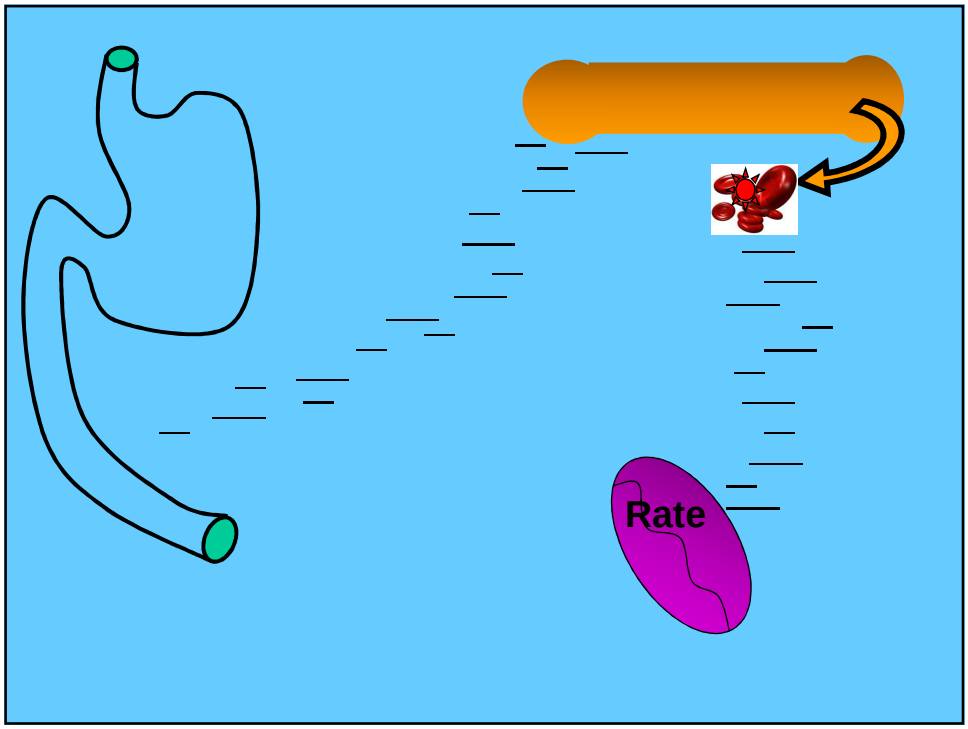
Fer héminique > Fer non héminique

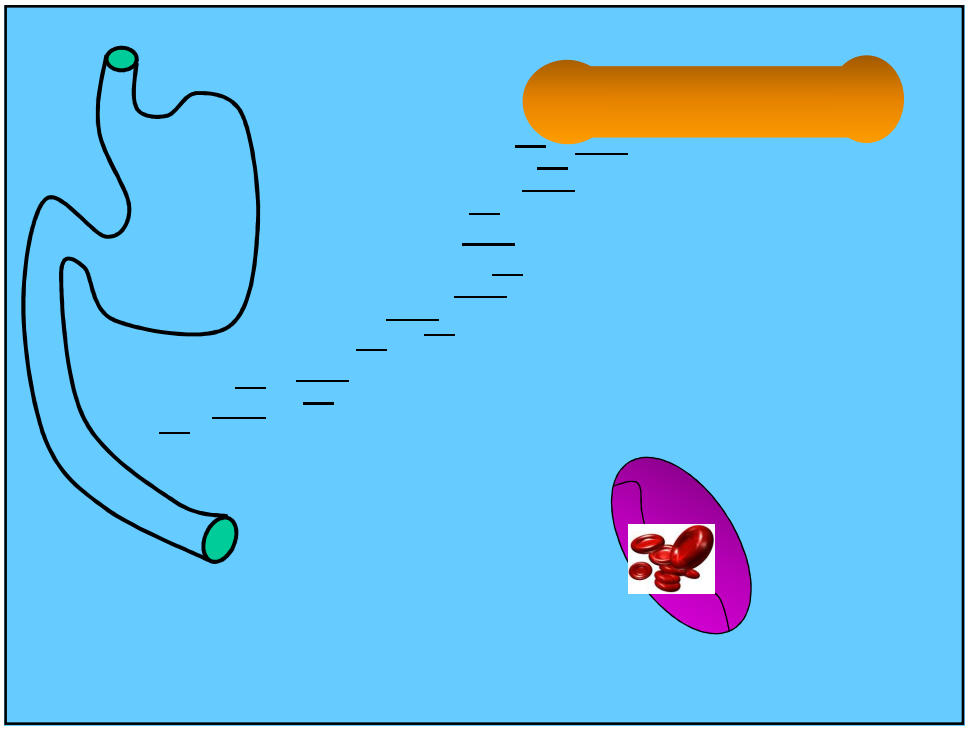
3. L'organisme humain est donc exposé au risque de manque de fer

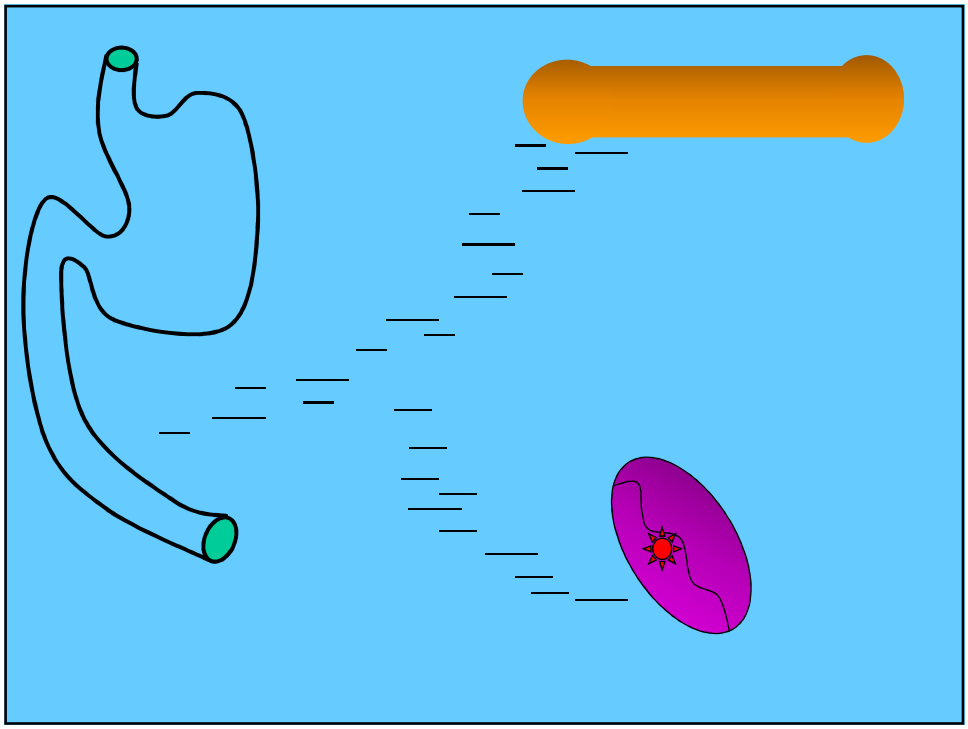
4. La destinée du fer alimentaire est essentiellement la moelle osseuse puis épouse celle du globule rouge



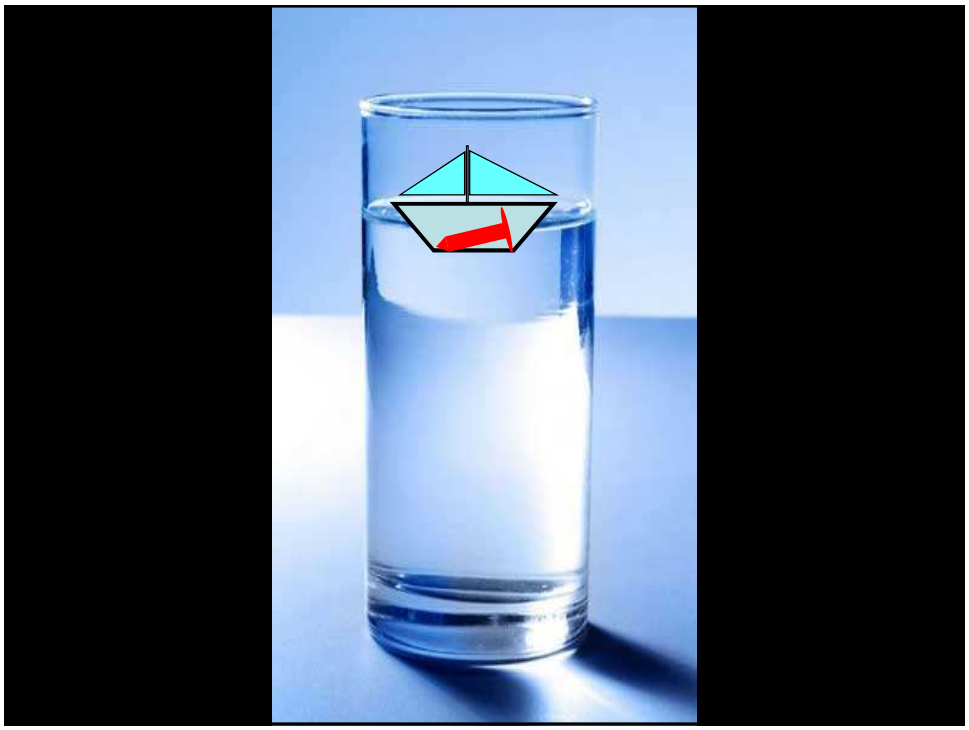

Moelle
osseuse

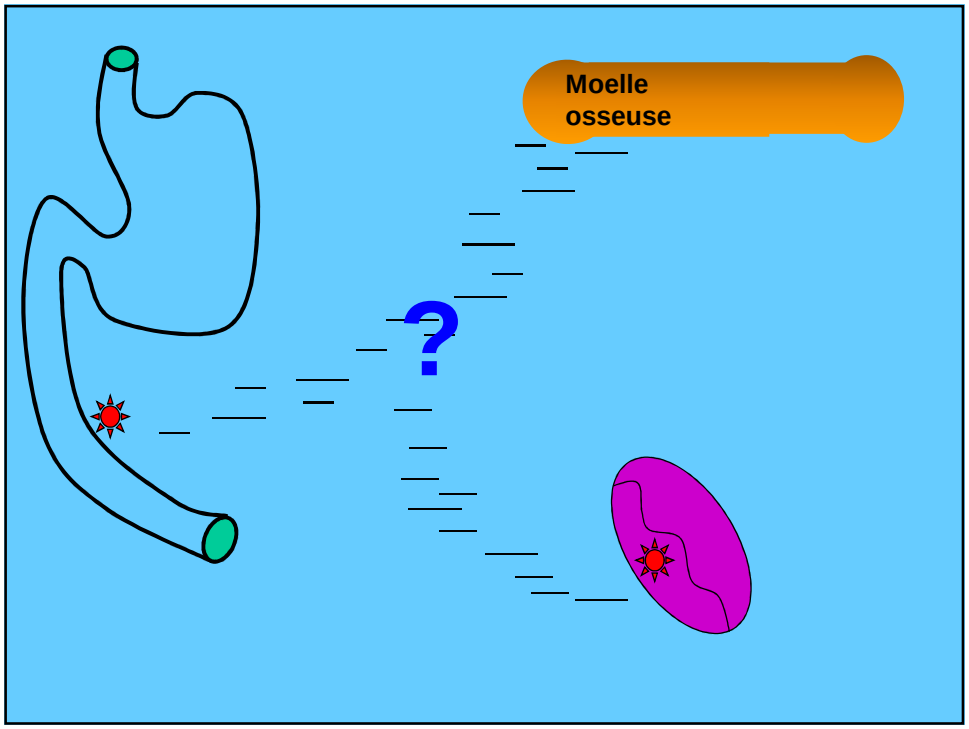

Rate

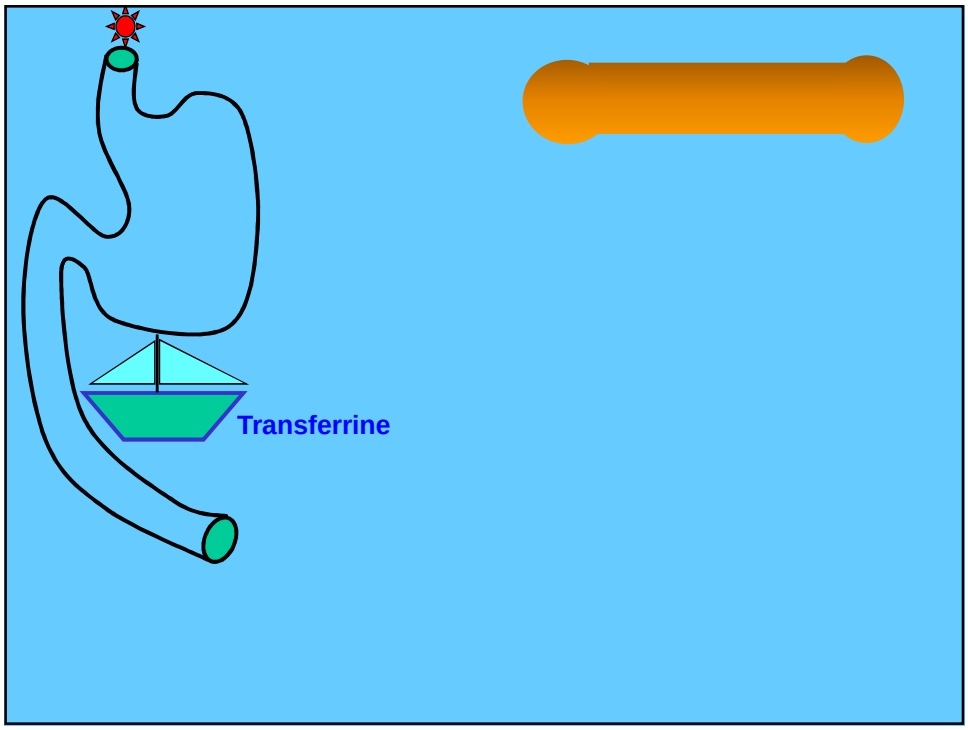


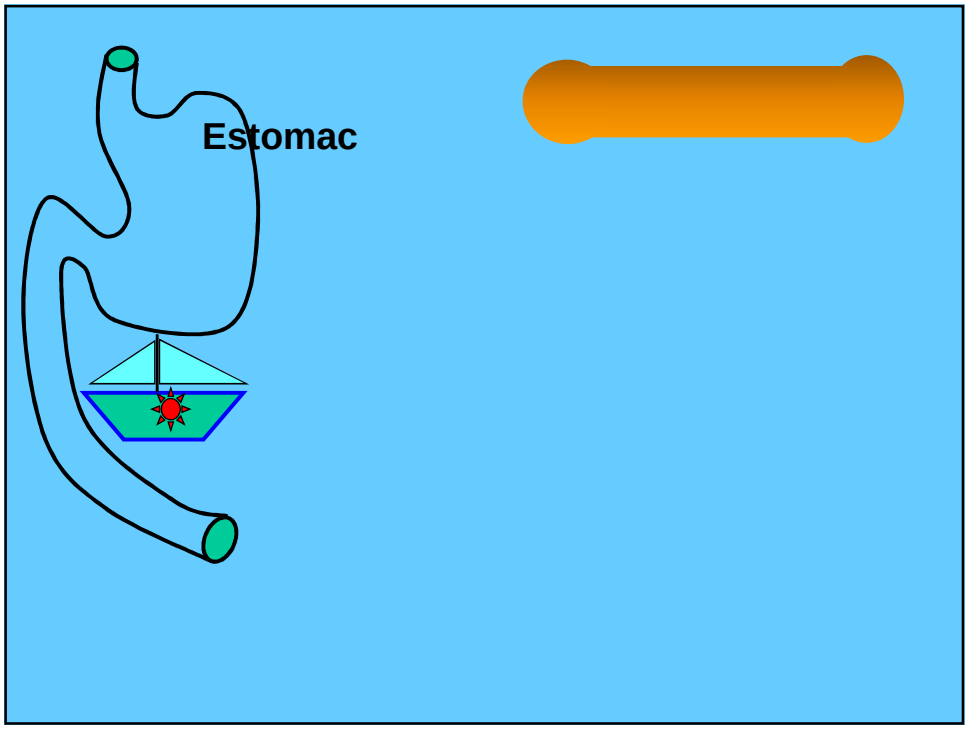


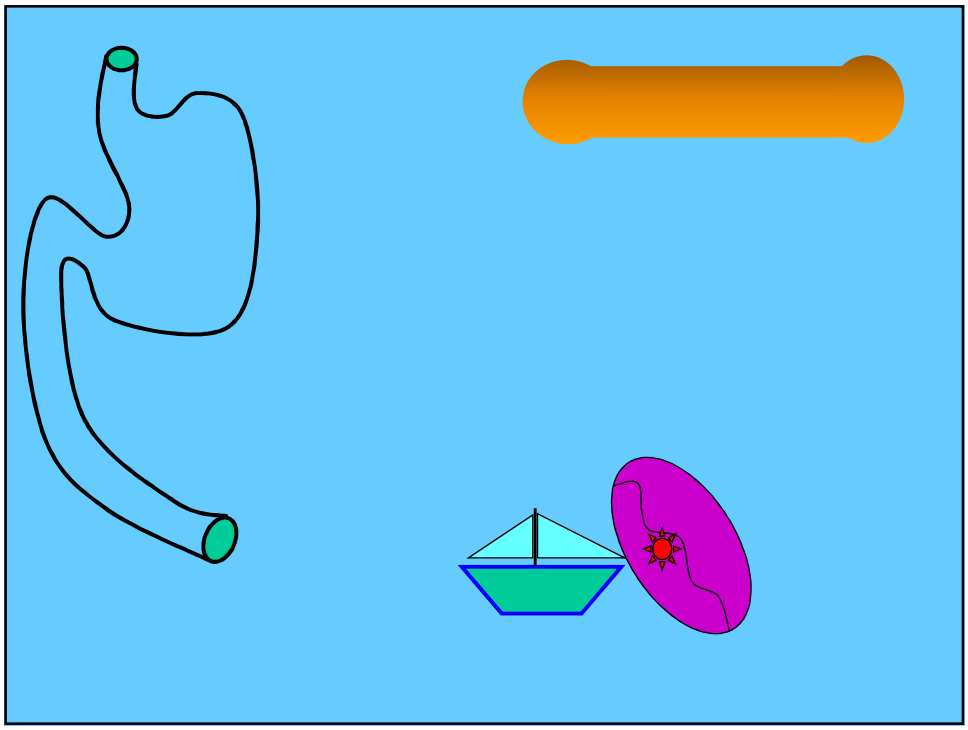
5. Le fer ne peut circuler dans le plasma et ne peut être stocké dans la cellule à l'état libre

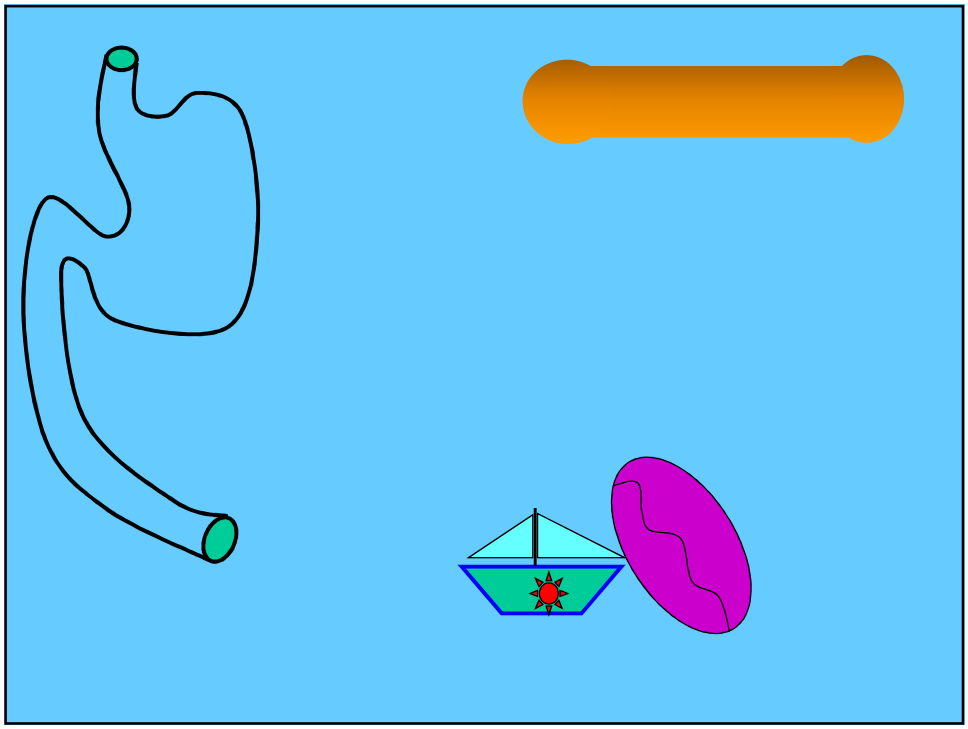


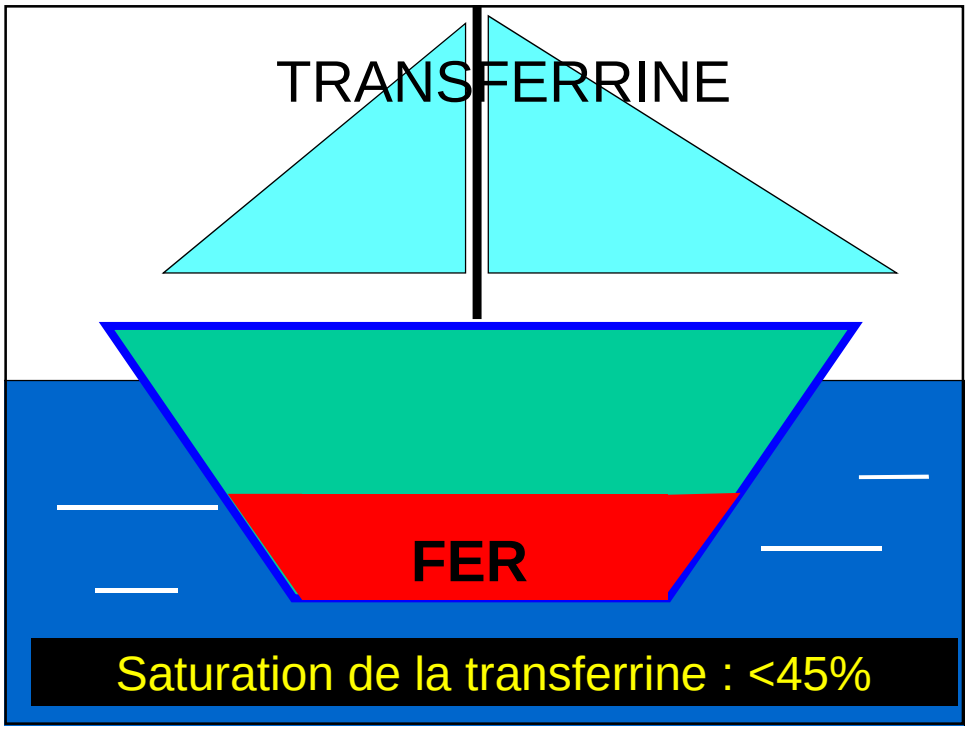

Moelle
osseuse
?

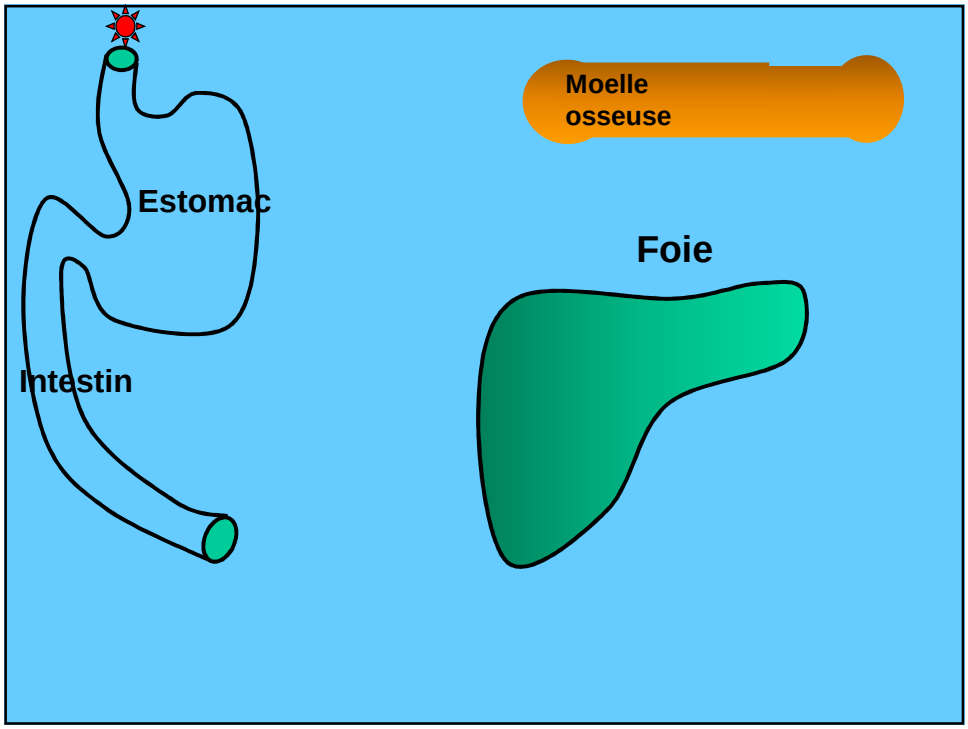

Transferrine

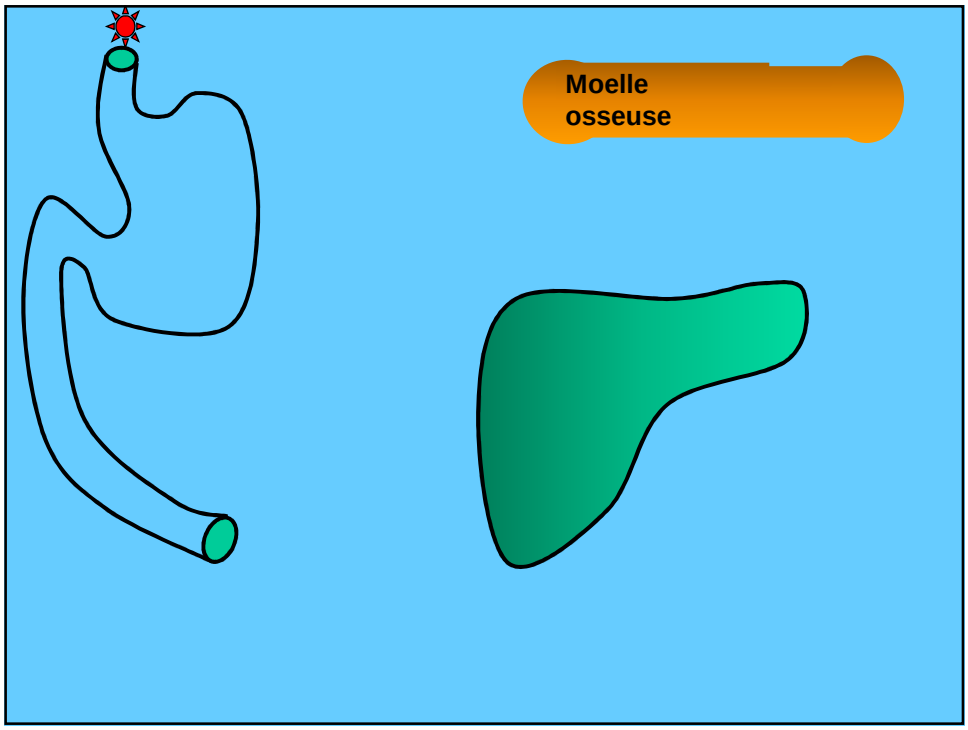

Estomac

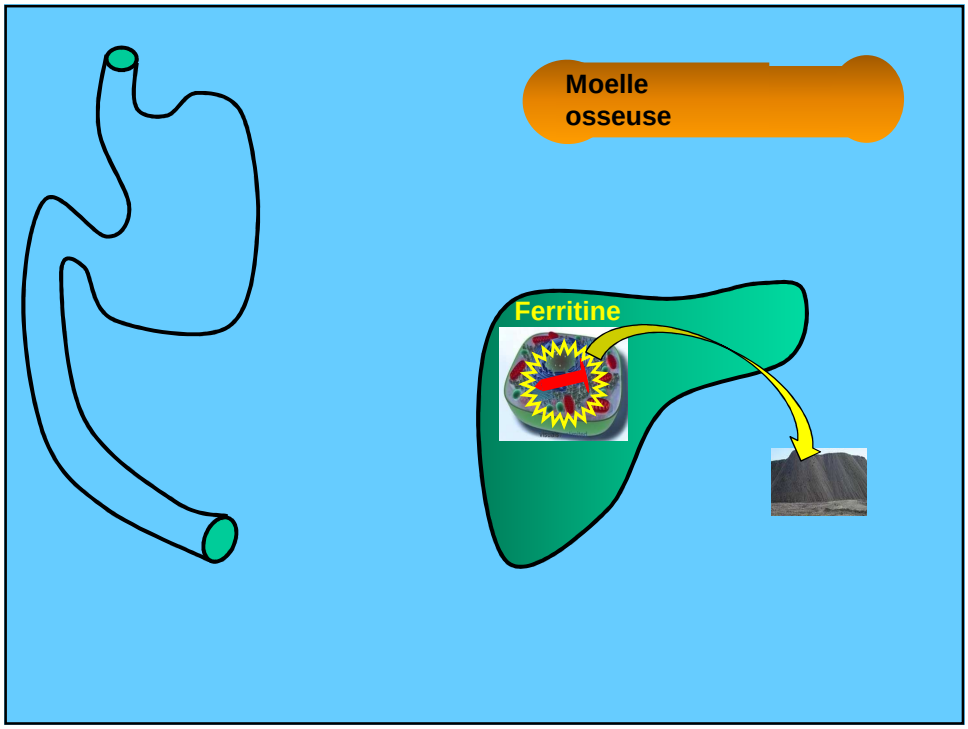


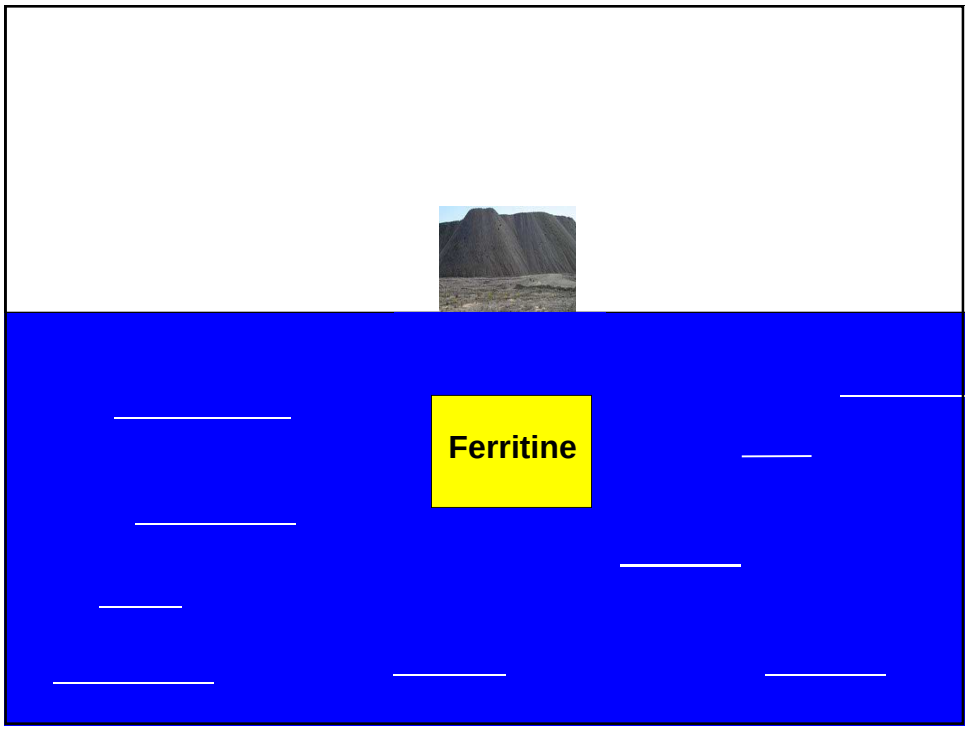



TRANSFERRINE
FER
Saturation de la transferrine : <45%


Moelle osseuse
Estomac
Foie
Intestin


Moelle
osseuse


Moelle
osseuse
Ferritine



6. La prise en compte de l ’état rédox du fer est capitale

Fer ferrique (Fe^{3+}) ⟷ Fer ferreux (Fe^{2+})

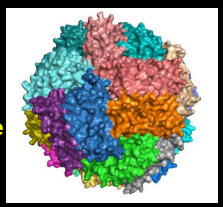
TRANSPORT ET STOCKAGE DU FER

Fer ferrique (Fe^{3+}) ⟷ Fer ferreux (Fe^{2+})

Transport plasmatique

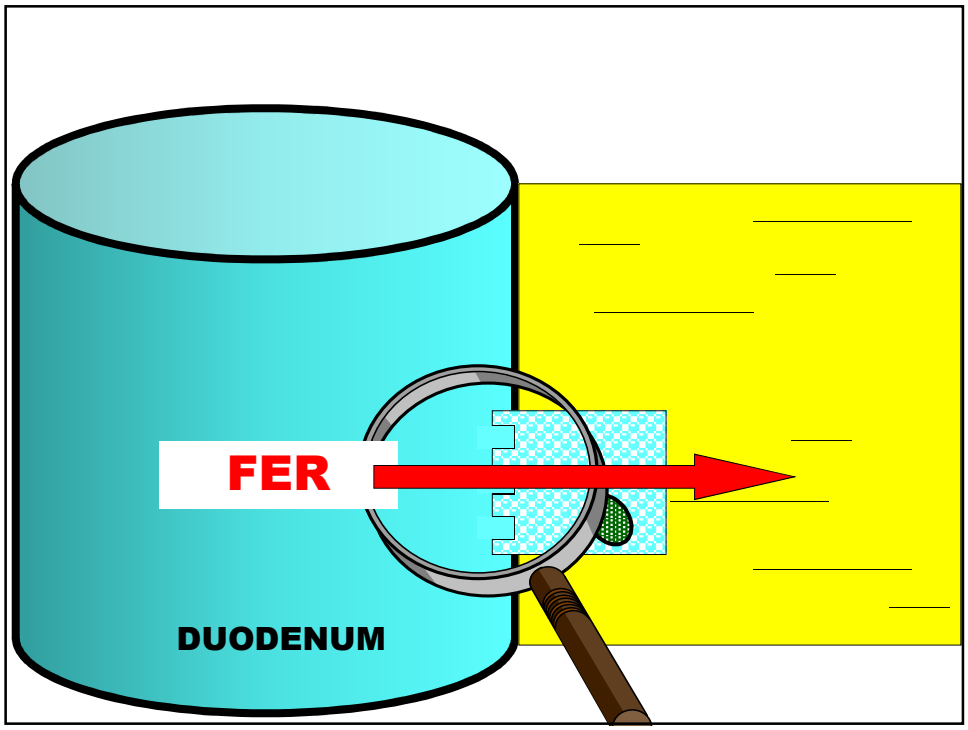
Transferrine

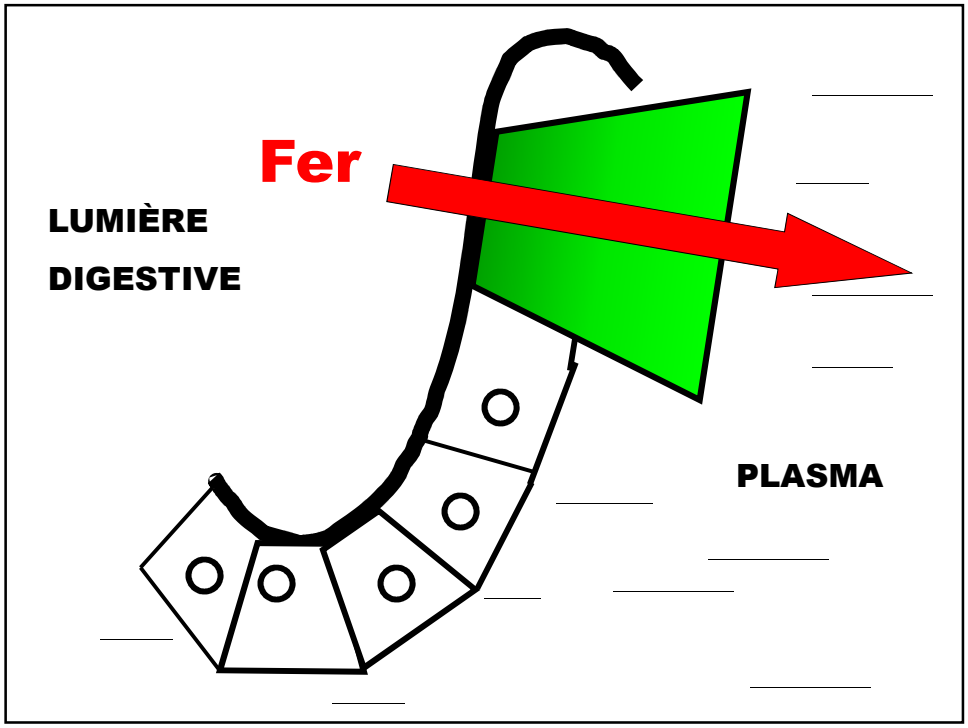
Stockage intracellulaire

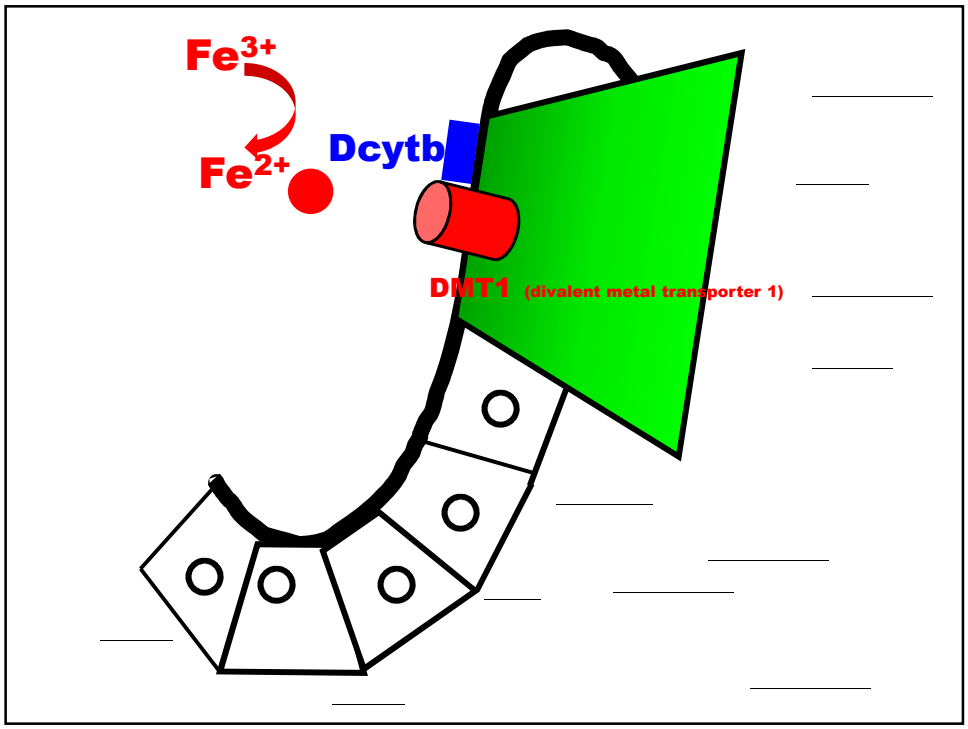


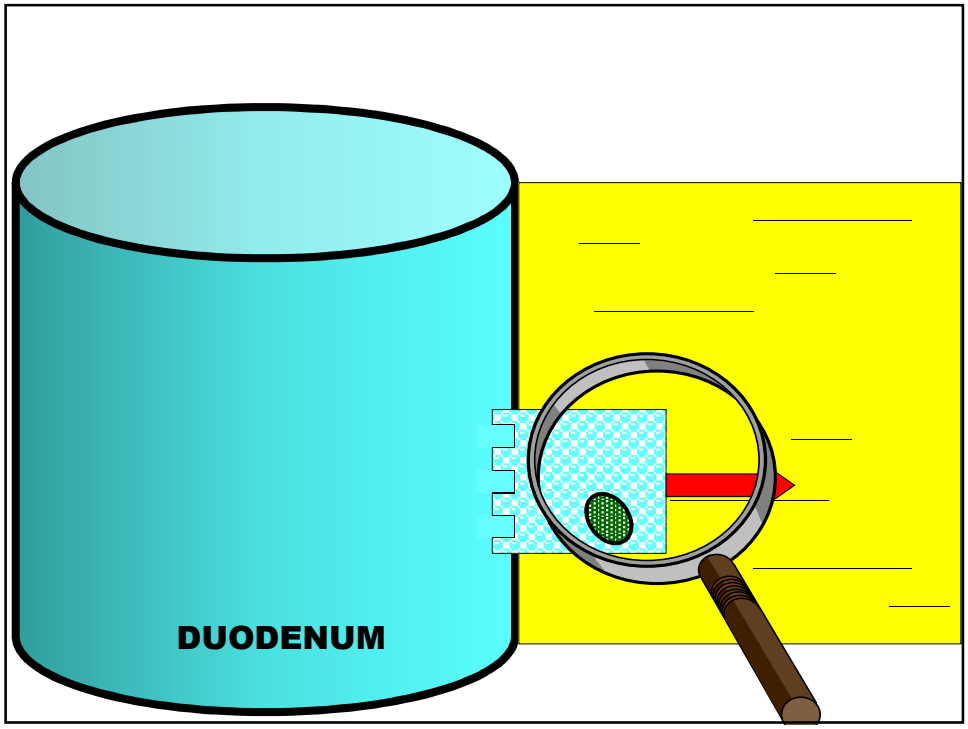
Ferritine

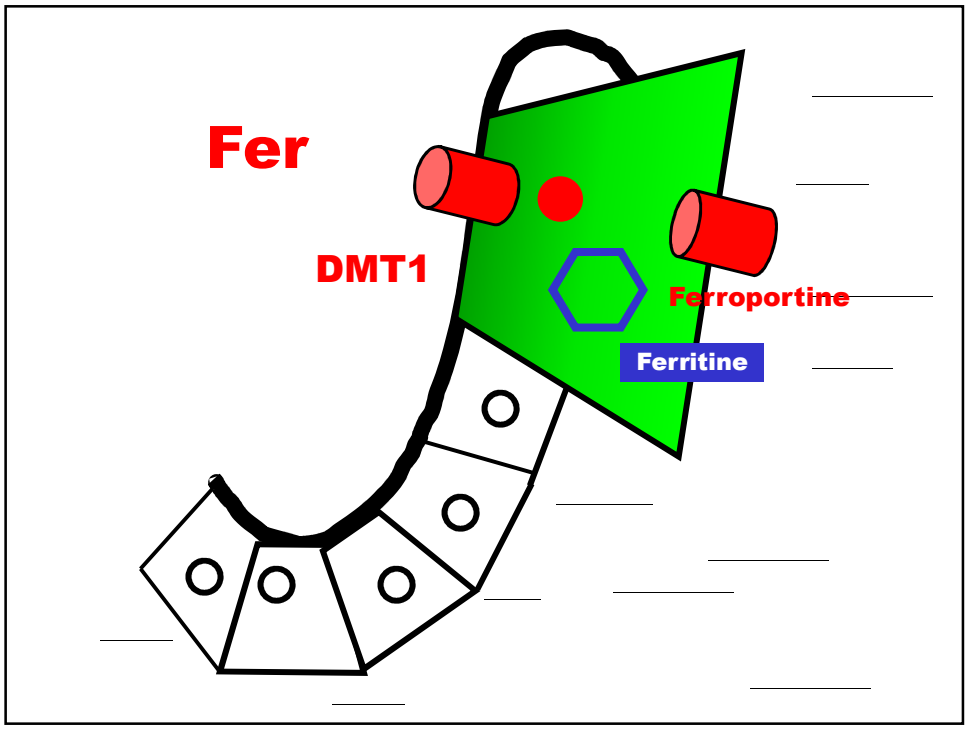
Transport transmembranaire

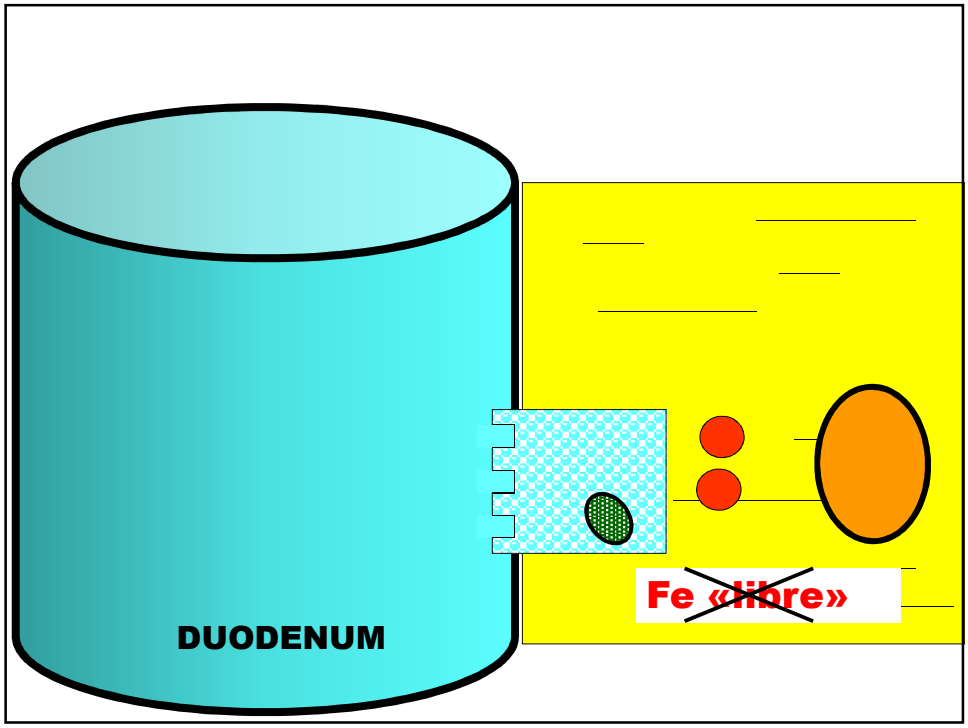

FER
DUODENUM

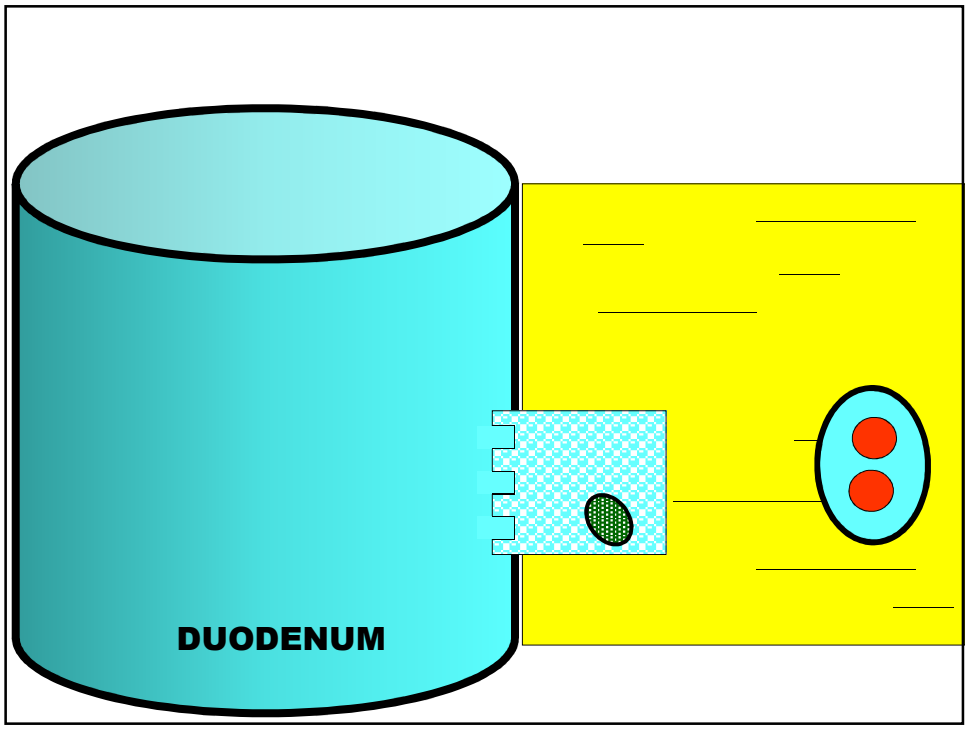

Fer
LUMIÈRE
DIGESTIVE
PLASMA

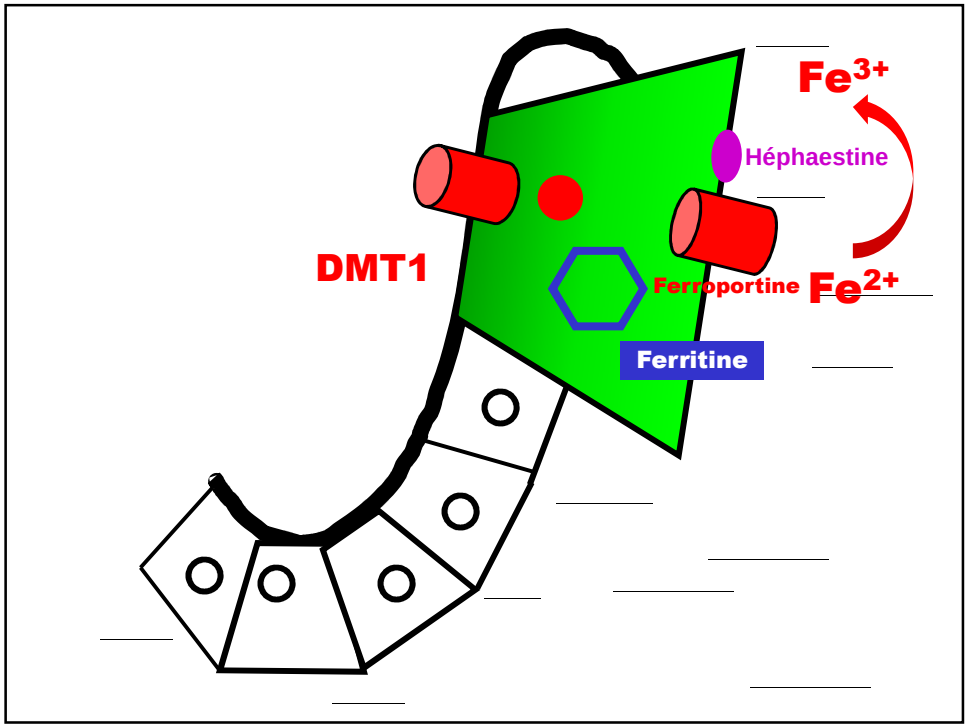

Fe3+
Fe2+
Dcytb
DMT1 (divalent metal transporter 1)

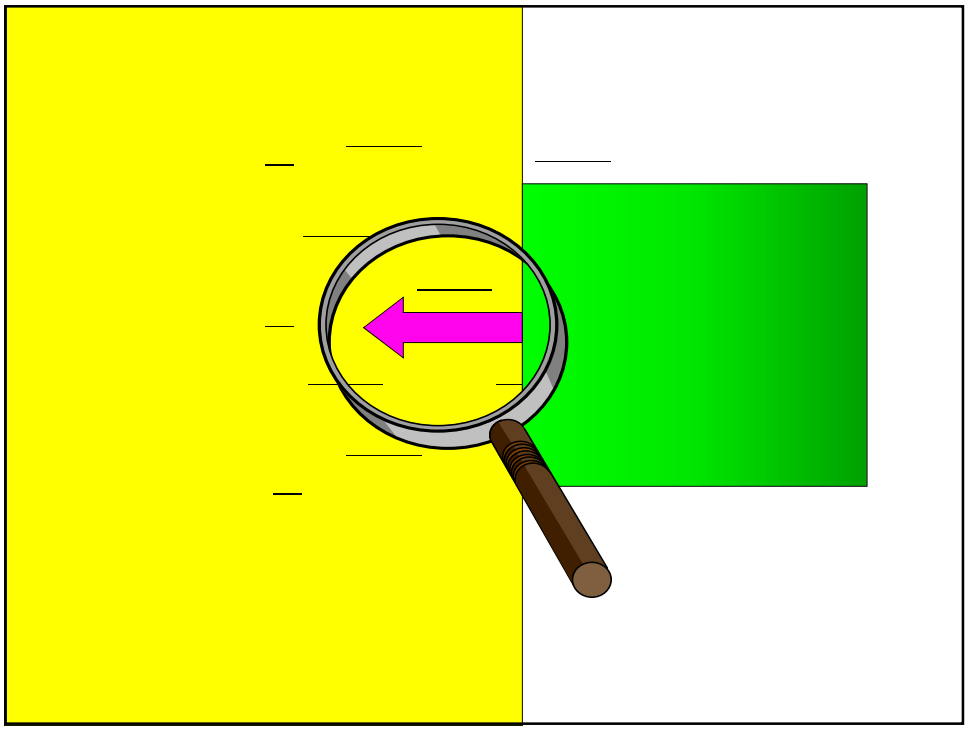

DUODENUM

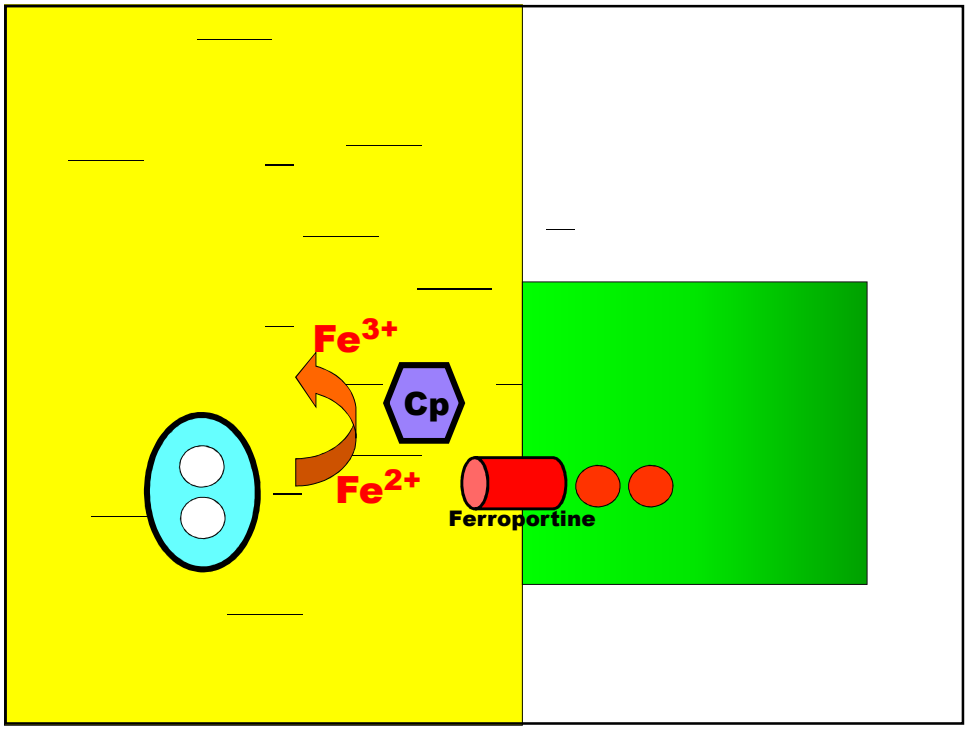

Fer
DMT1
Ferroportine
Ferritine

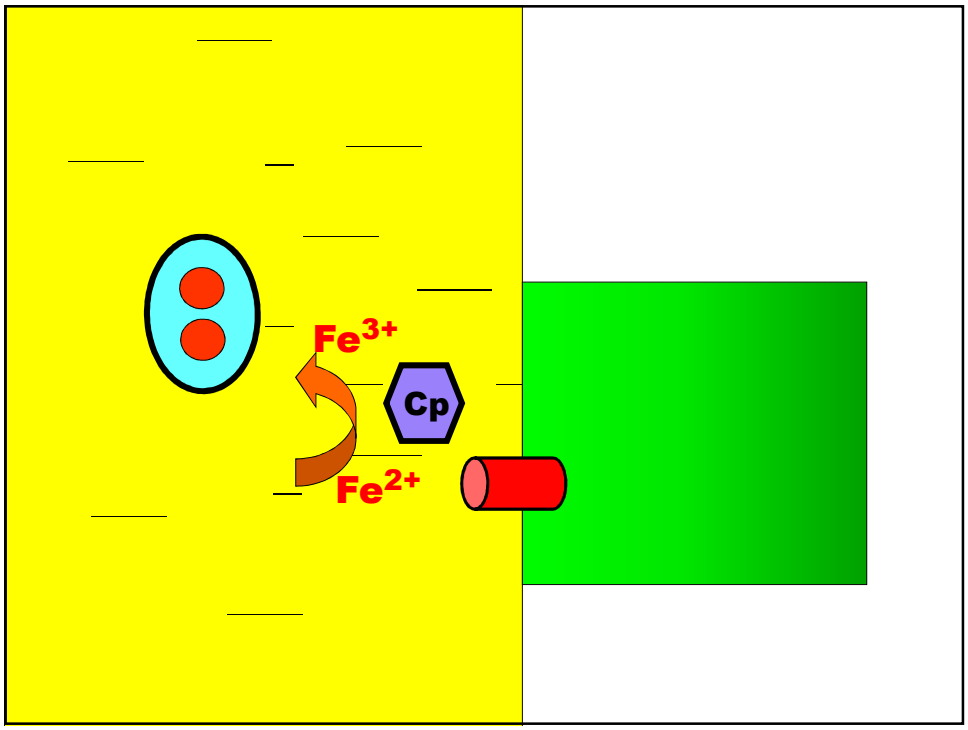

DUODENUM
Fe «libre»


DUODENUM


Fe3+
Héphaestine
DMT1
Ferroportine
Fe2+
Ferritine



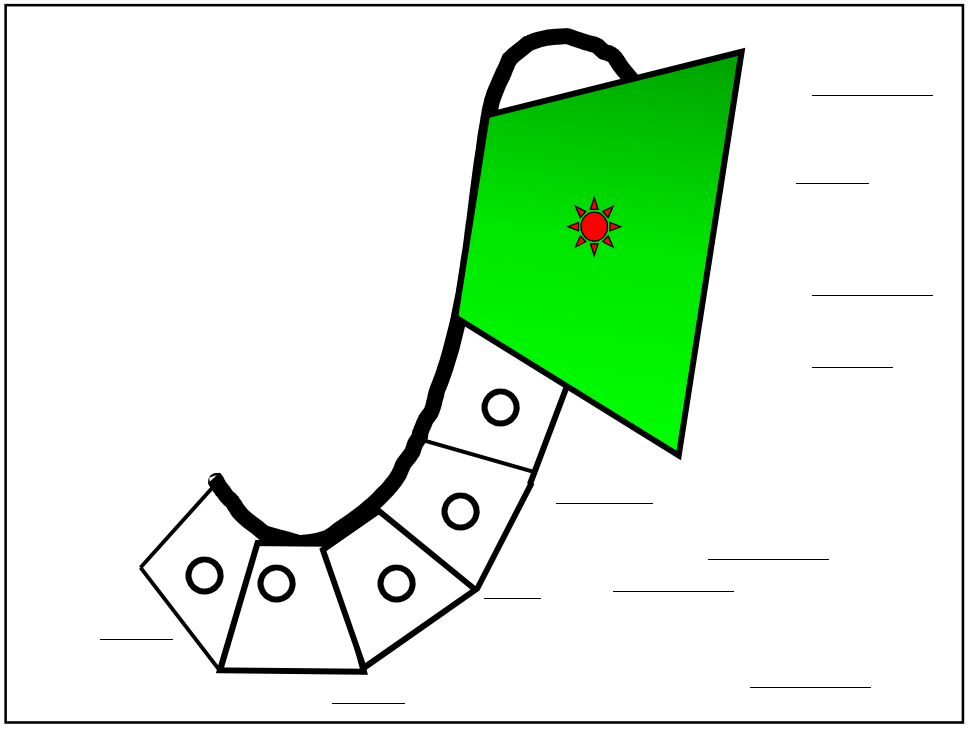

Fe3+
Cp
Fe2+
Ferroportine

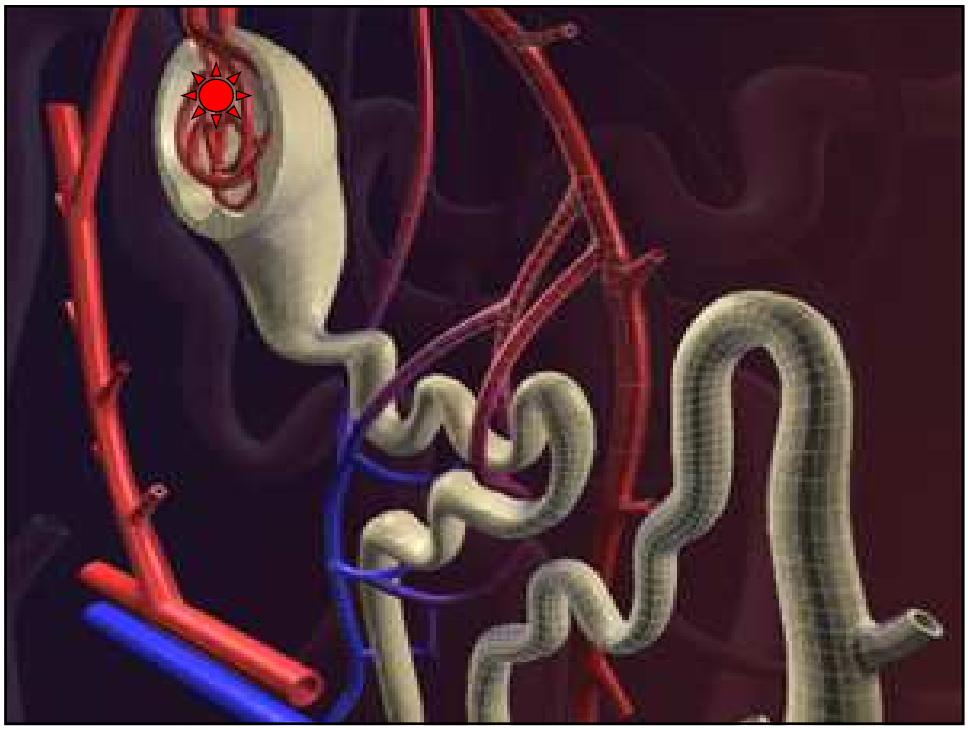


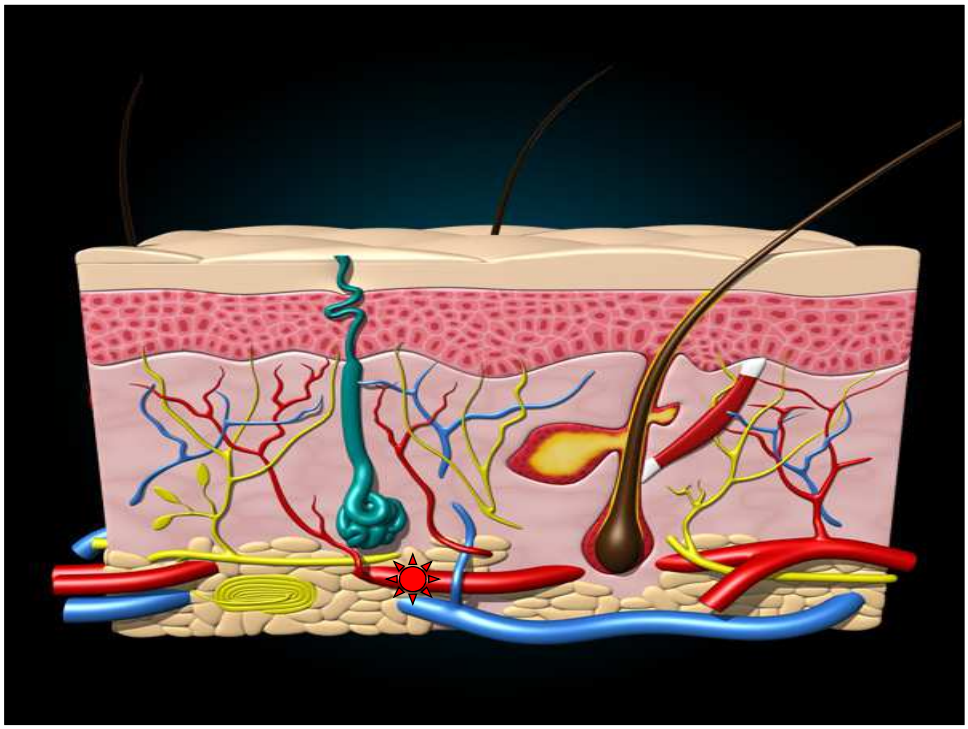
Fer ferrique (Fe^{3+}) ⟷ Fer ferreux (Fe^{2+})

TOXICITE DU FER

7. L’organisme humain est très peu armé pour excréter le fer



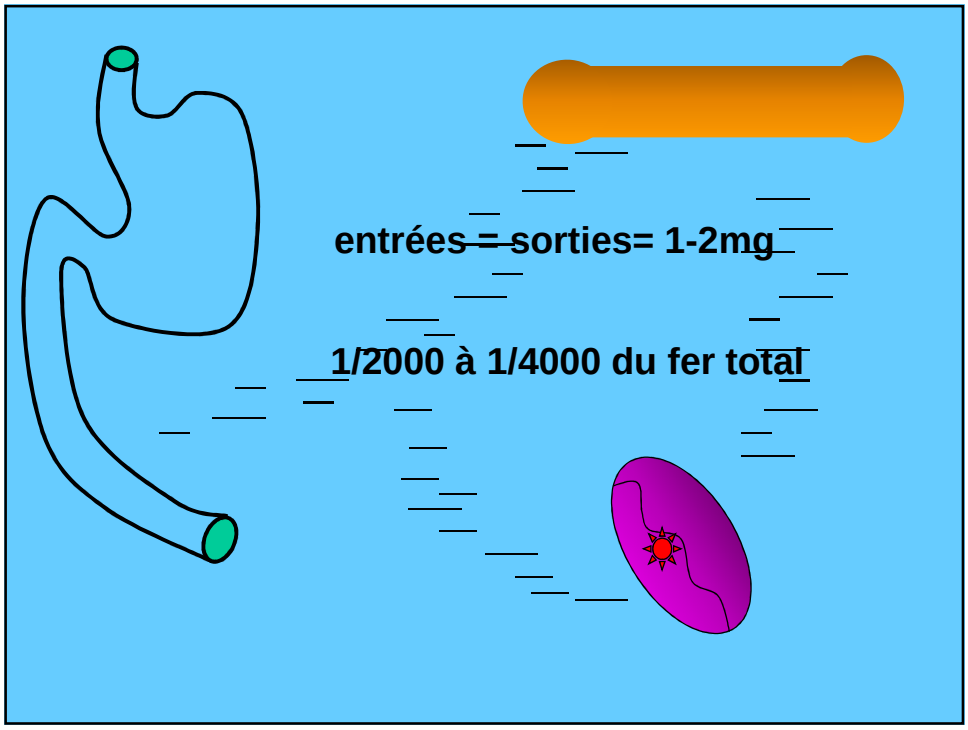




1-2mg /jour…

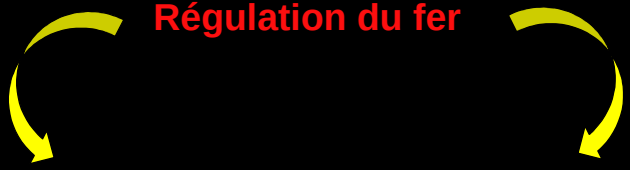
8. L’organisme humain est donc très exposé au risque de surcharge en fer

9. Le fer est un pionnier du recyclage…



10. La vulnérabilité de l'organisme à l'insuffisance comme à l'excès de fer explique l'extrême finesse de la régulation du fer

Régulation du fer

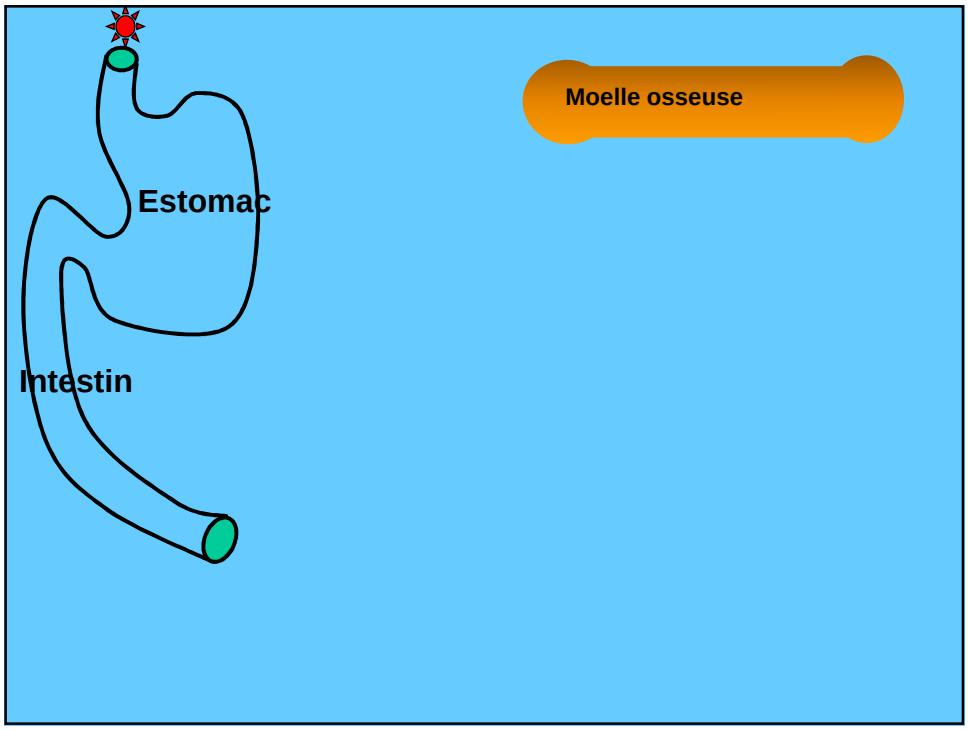


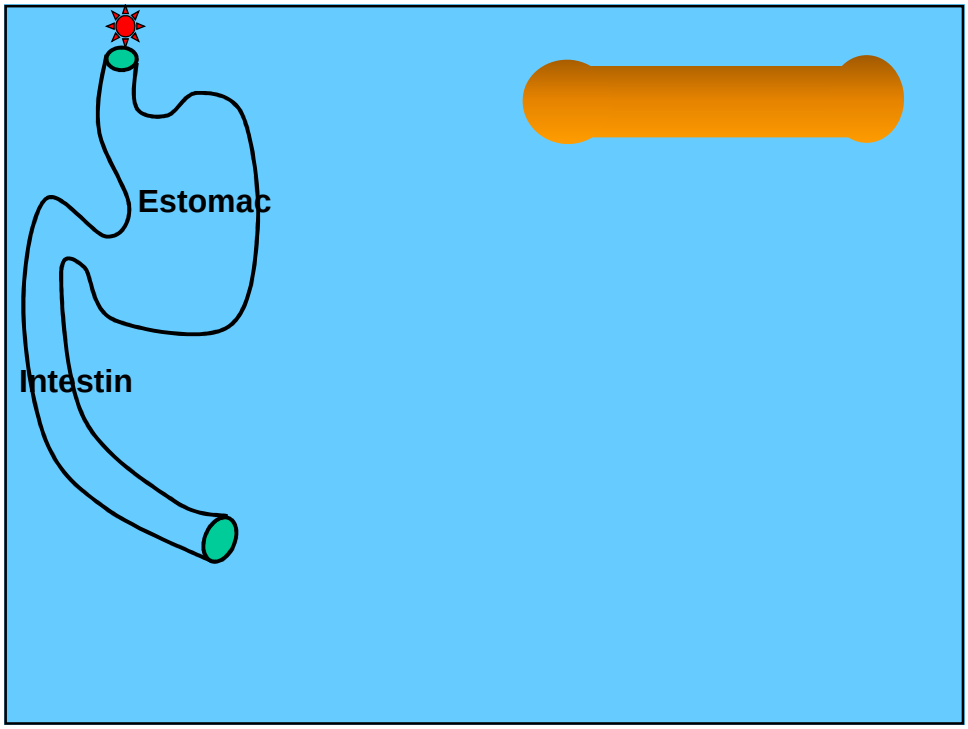
Régulation générale

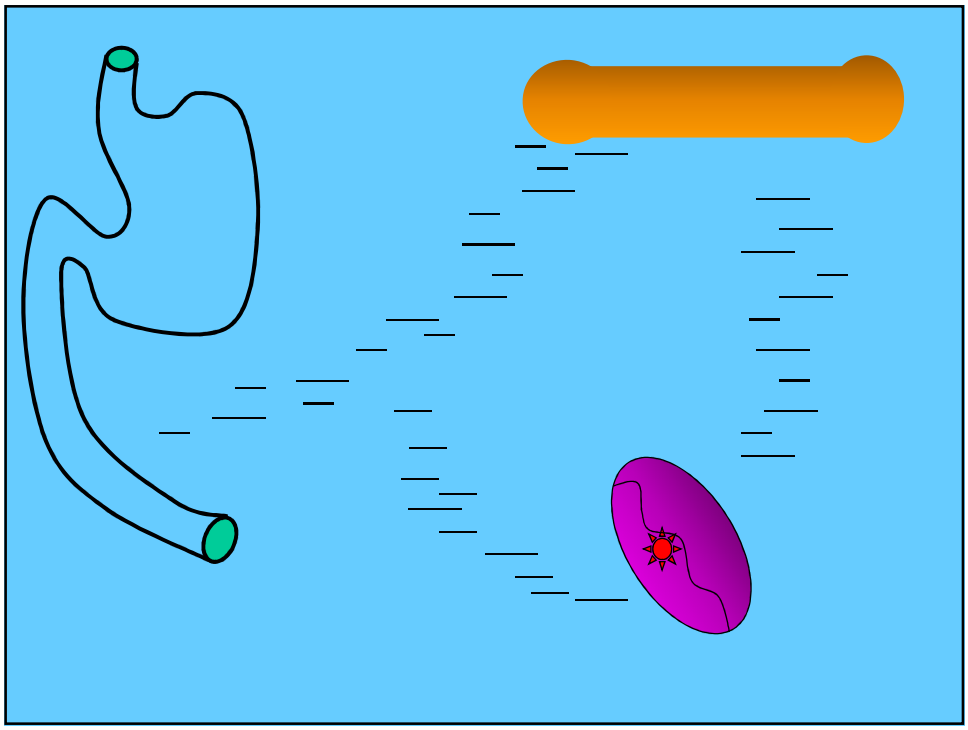
Régulation locale

= Régulation «systémique»

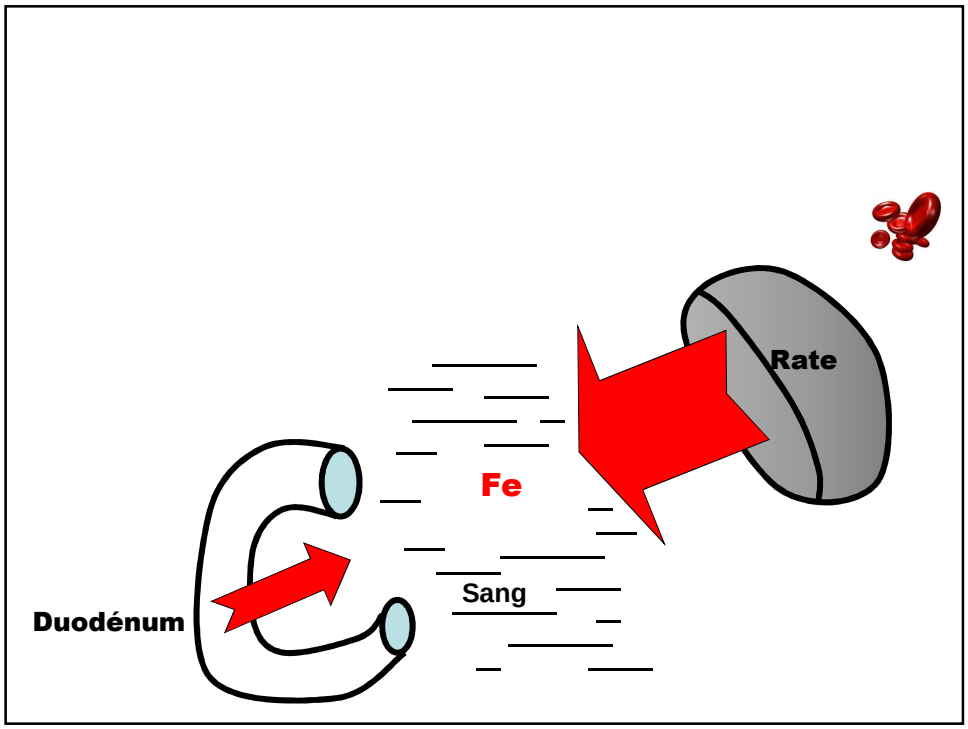
= Régulation «intracellulaire»

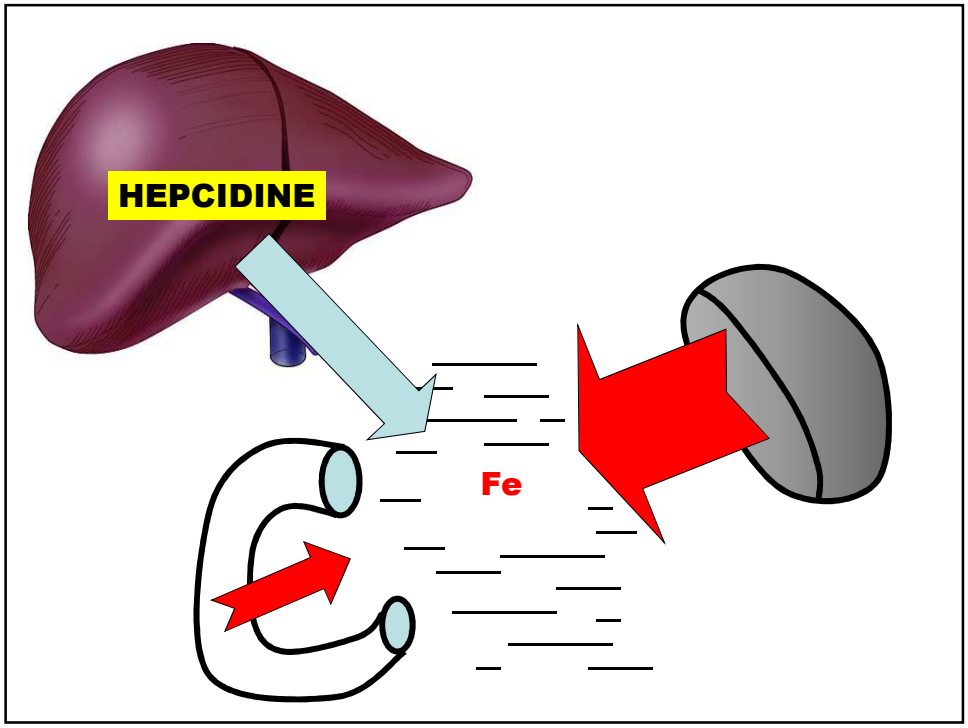

Moelle osseuse
Estomac
Intestin

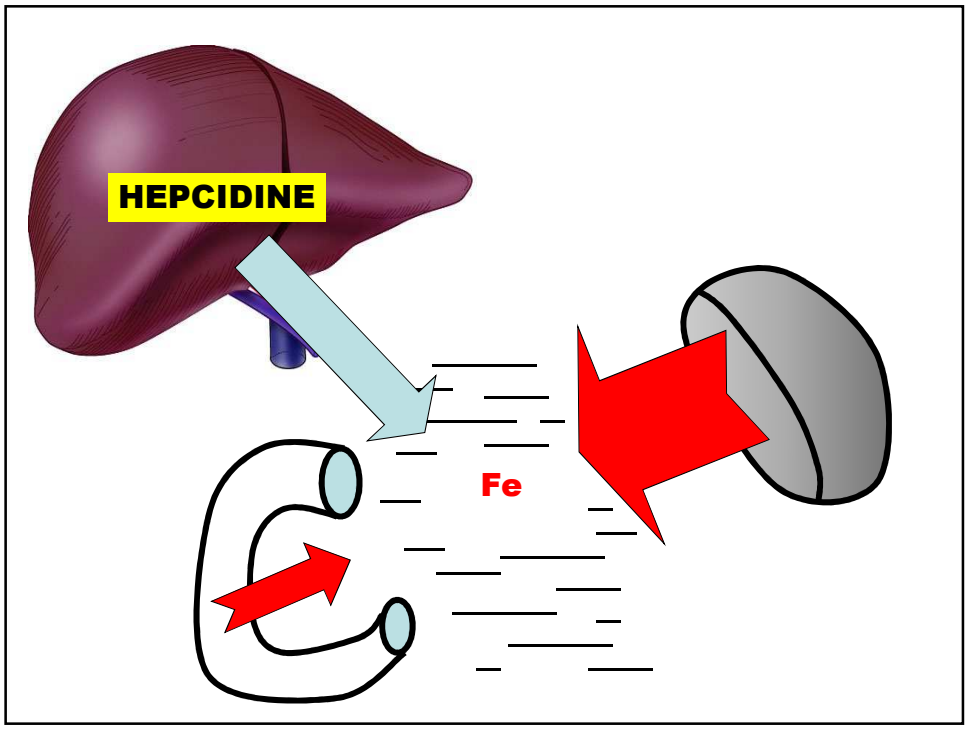

Estomac
Intestin

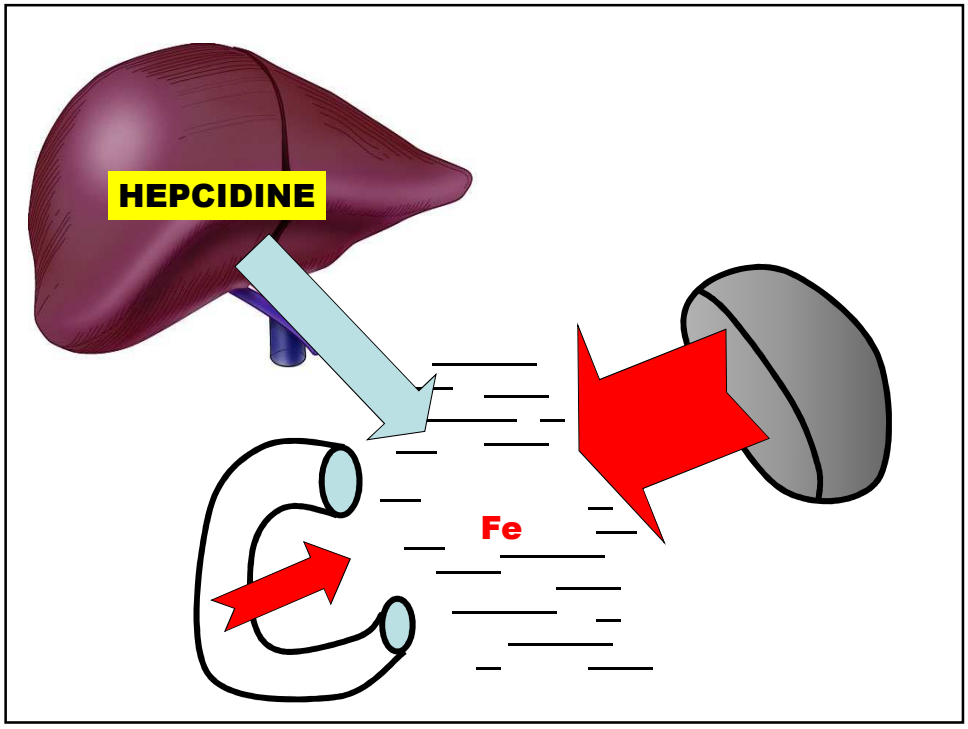


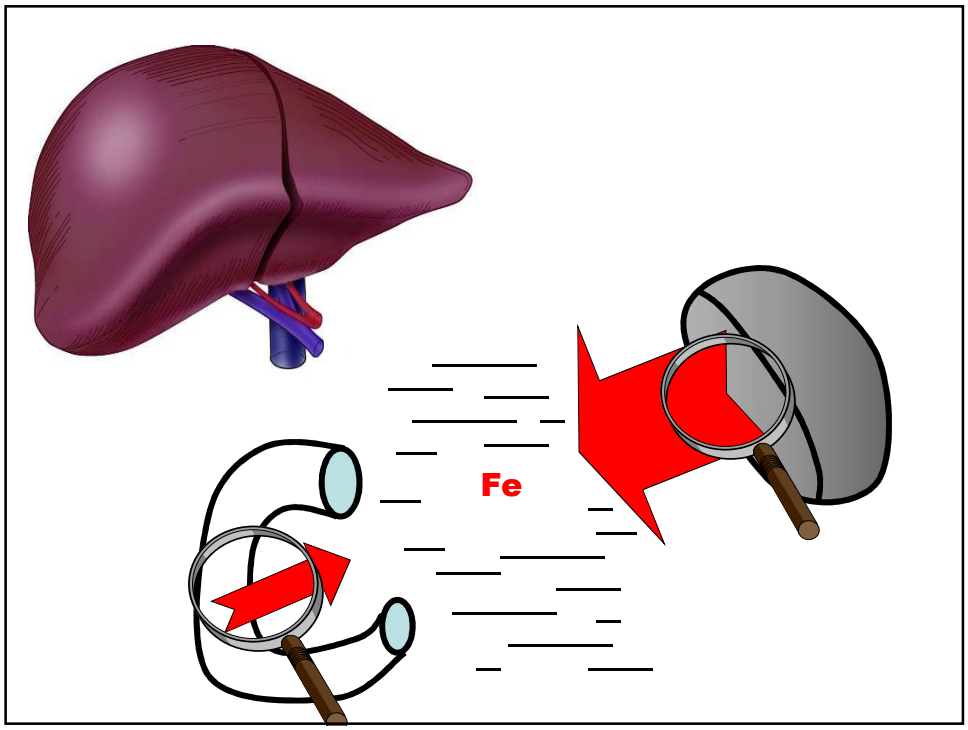
L’hepcidine : hormone de régulation du fer

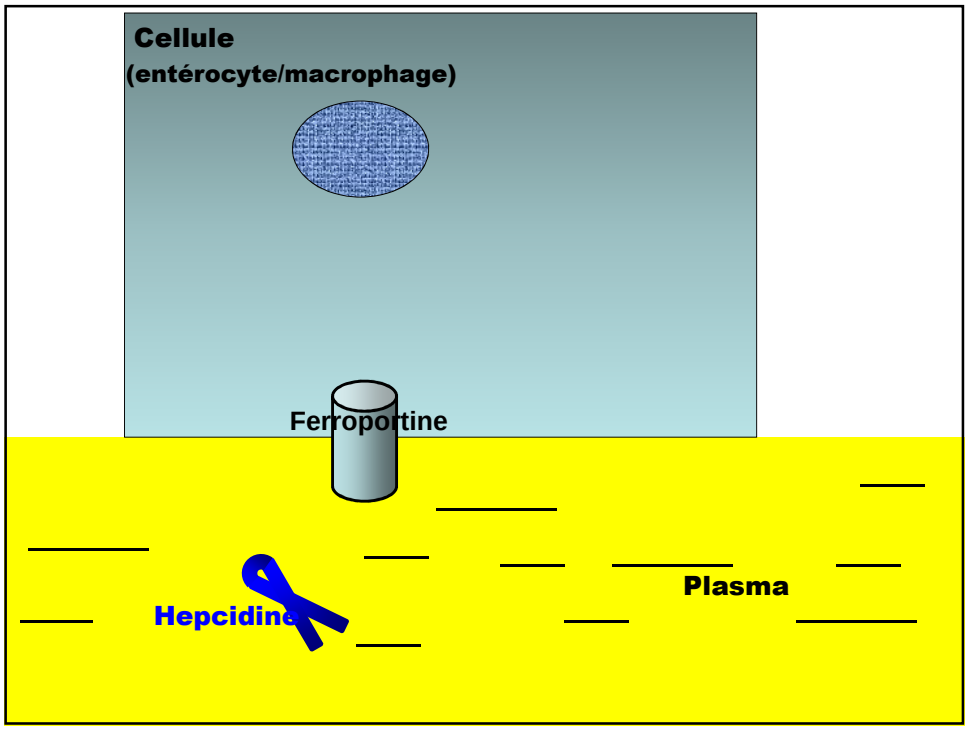

Rate
Fe
Sang
Duodénum

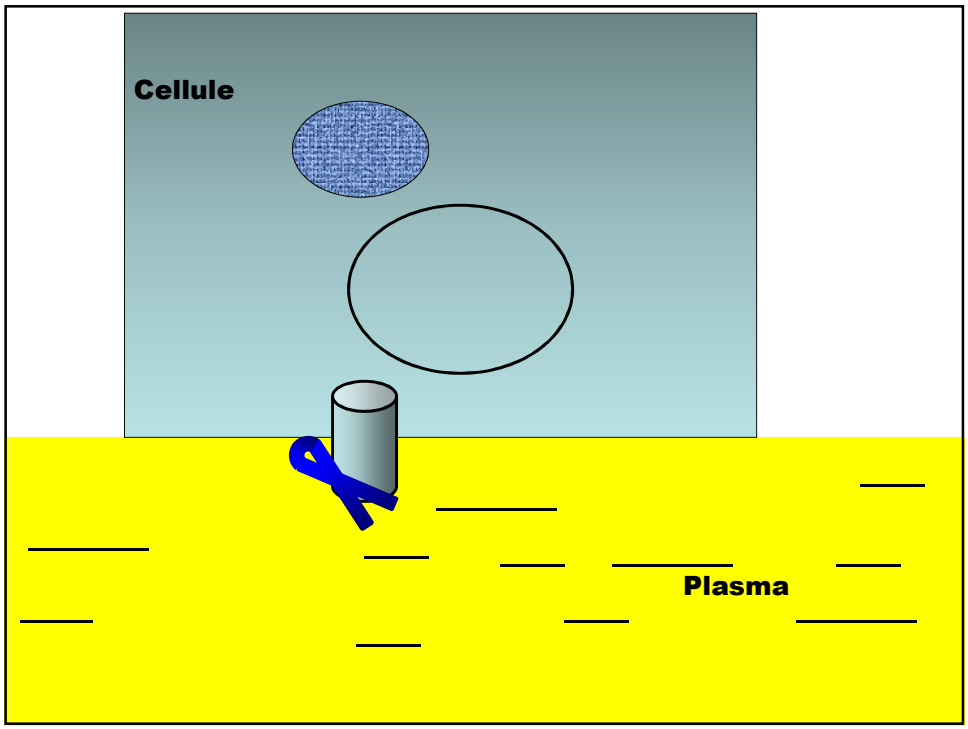

HEPCIDINE
Fe

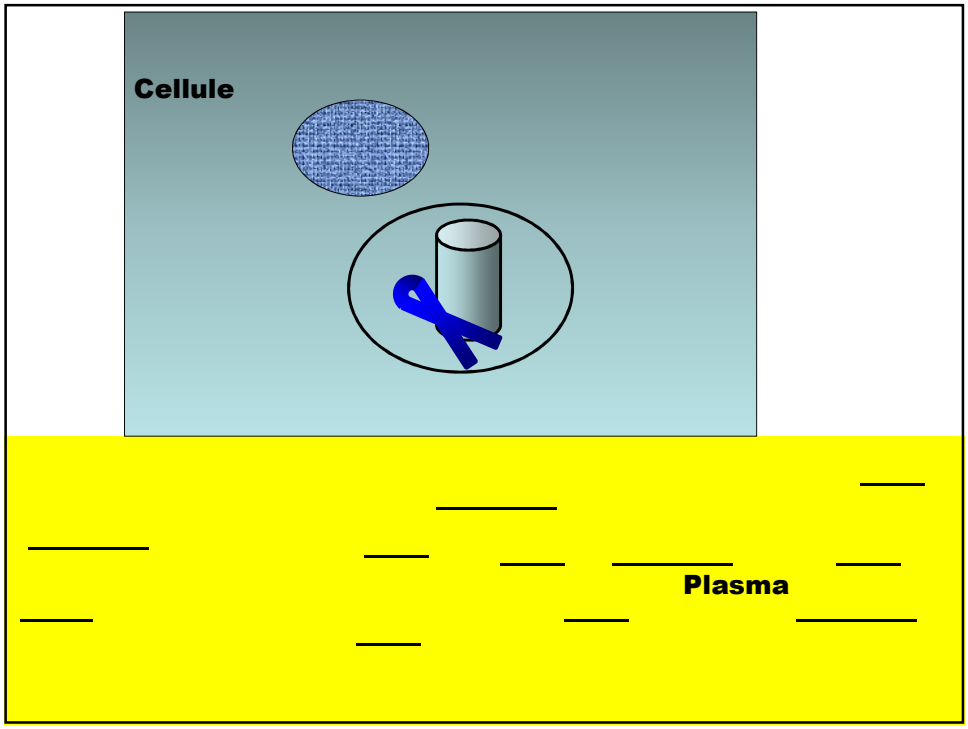

HEPCIDINE
Fe

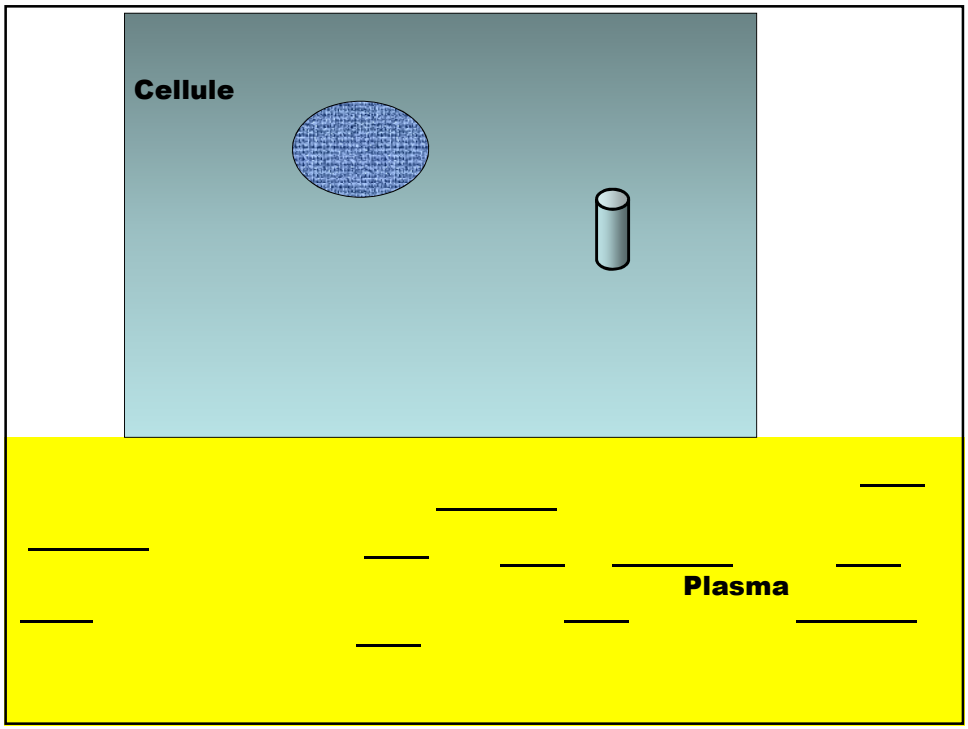

HEPCIDINE
Fe

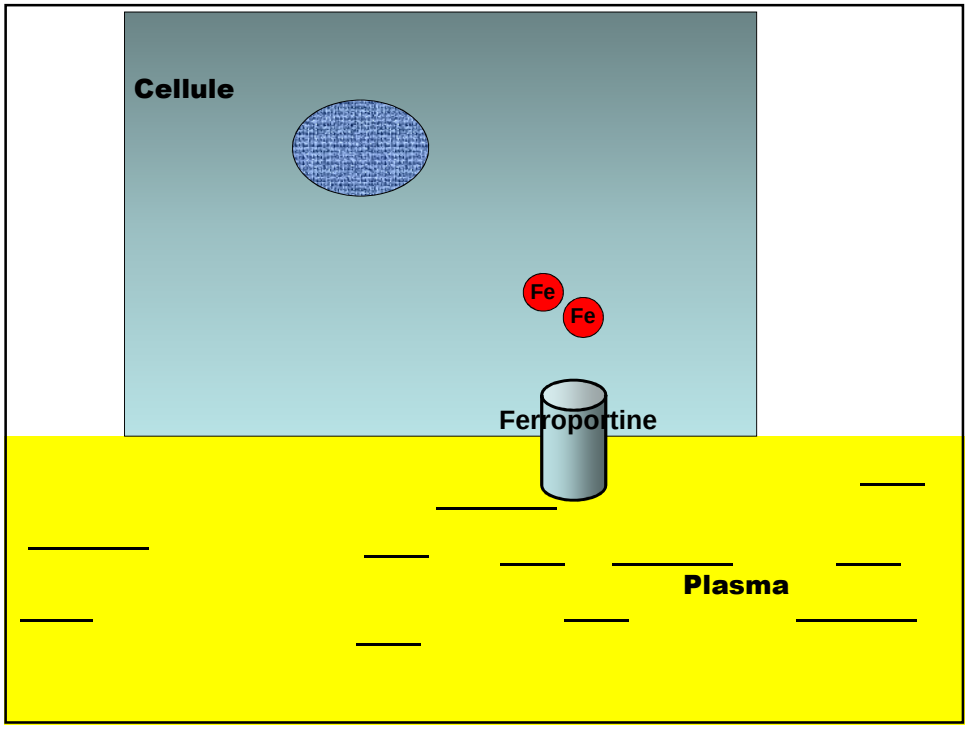

Fe

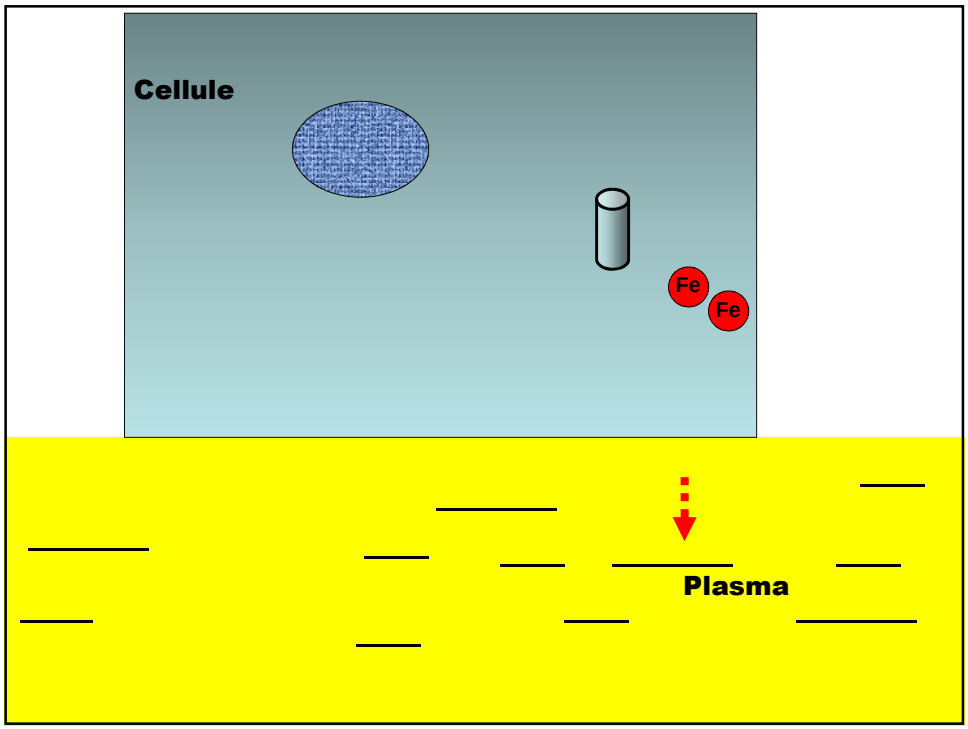

Cellule
(entérocyte/macrophage)
Ferroportine
Plasma
Hepcidine

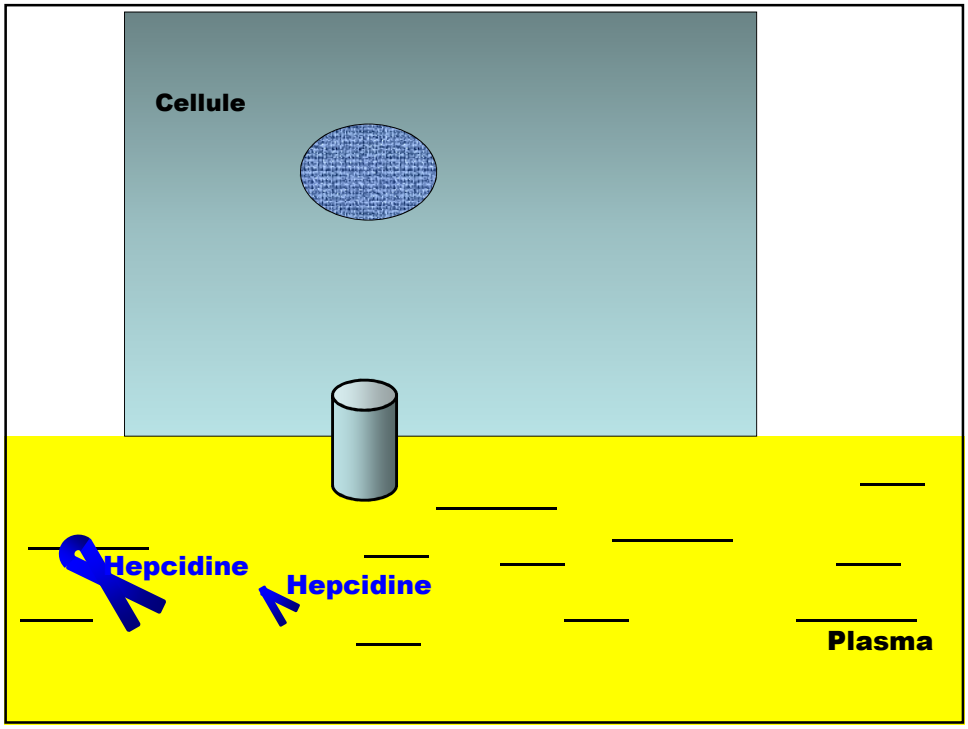

Cellule
Plasma

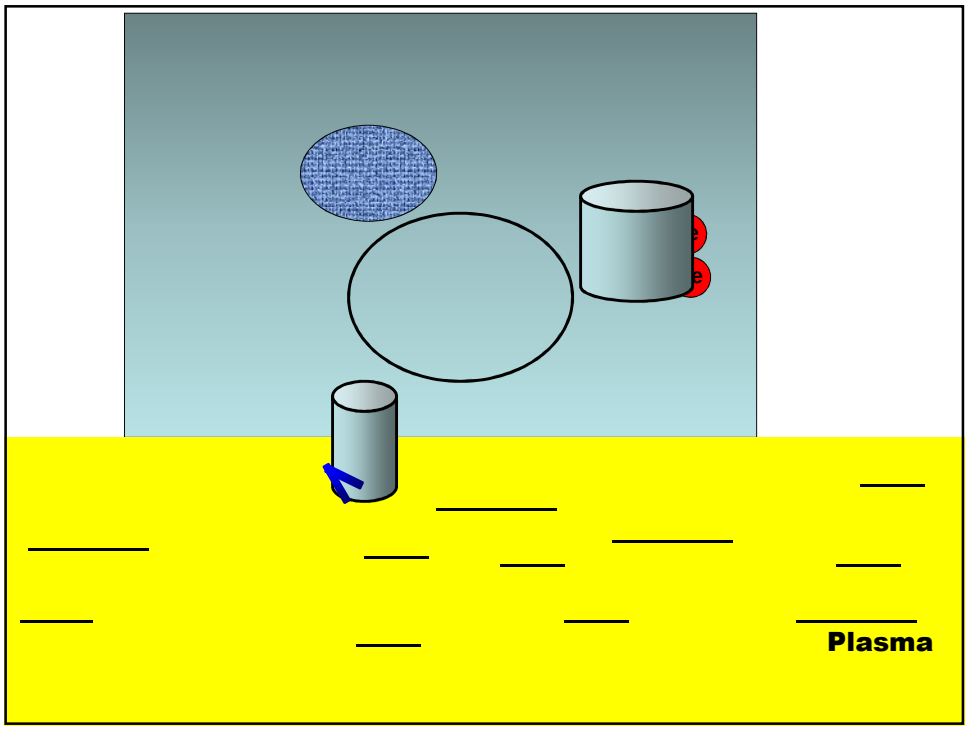

Cellule
Plasma


Cellule
Plasma

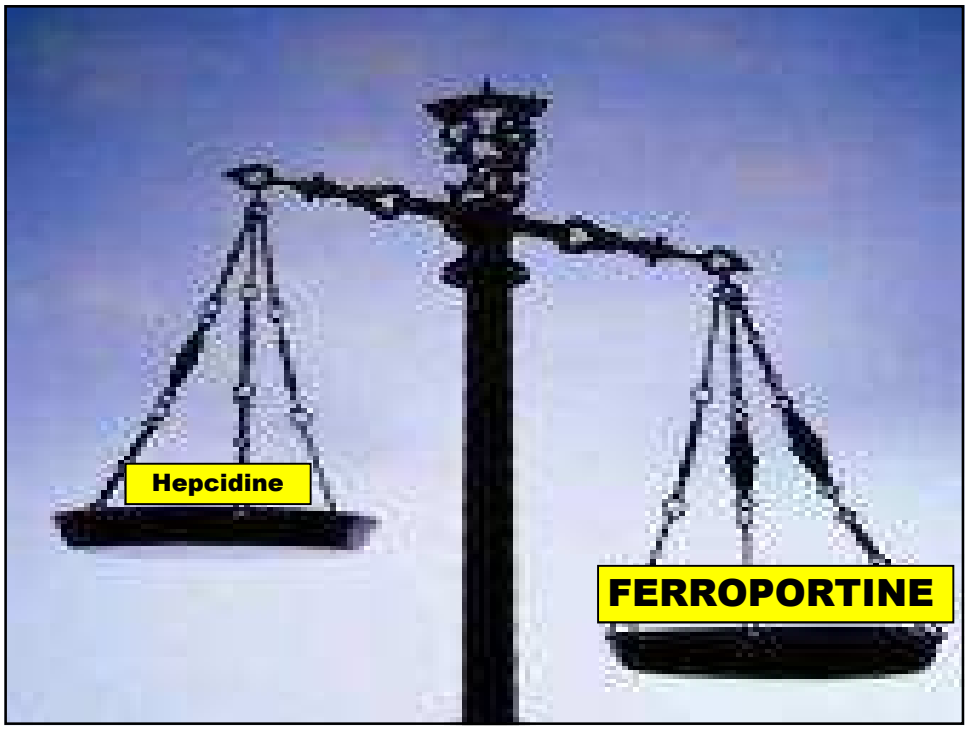

Cellule
Fe
Fe
Ferroportine
Plasma

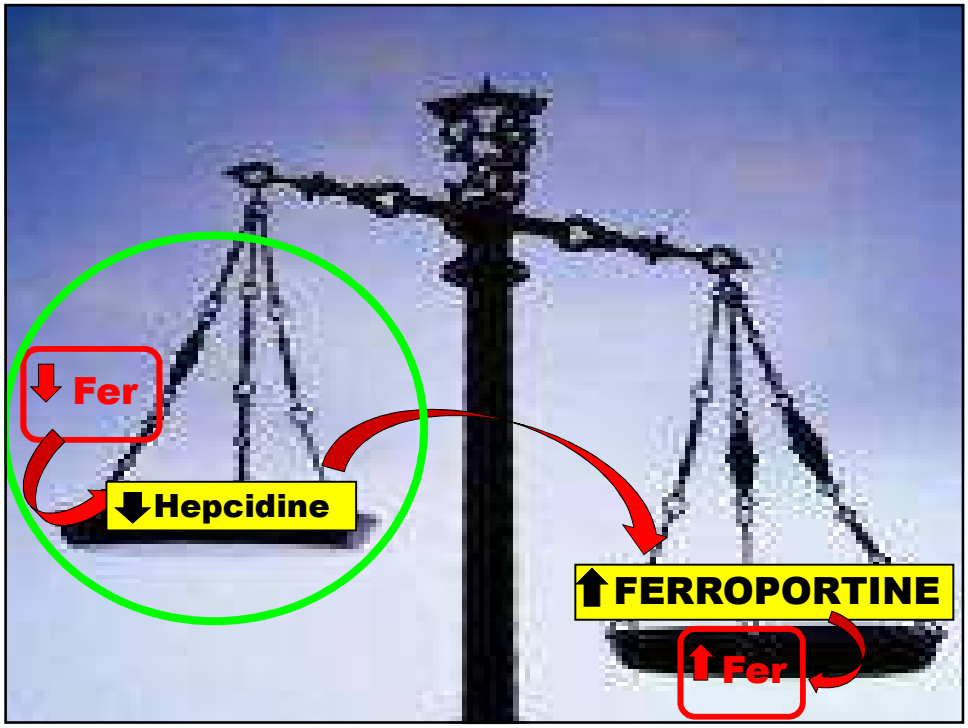

Cellule
Fe
Fe
Plasma

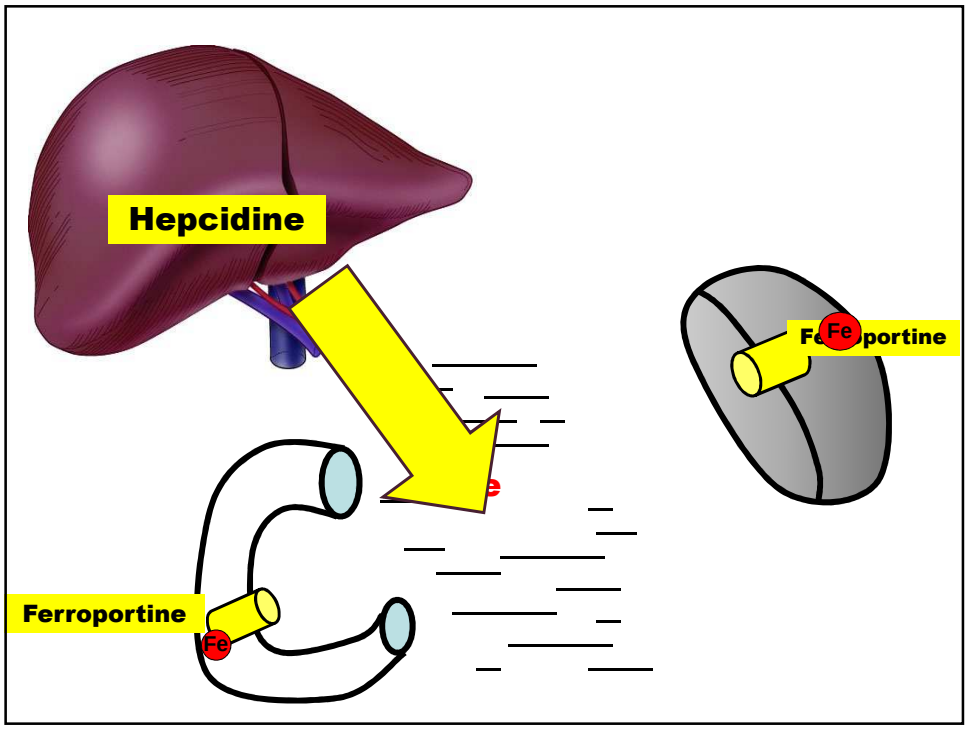

Cellule
Hepcidine
Hepcidine
Plasma

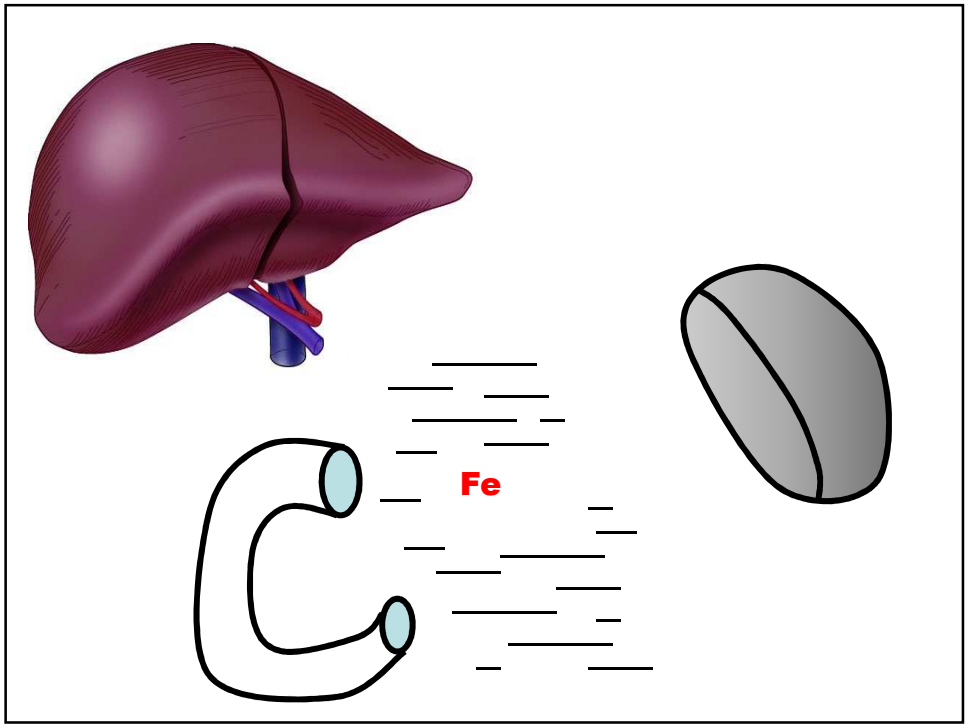

Plasma

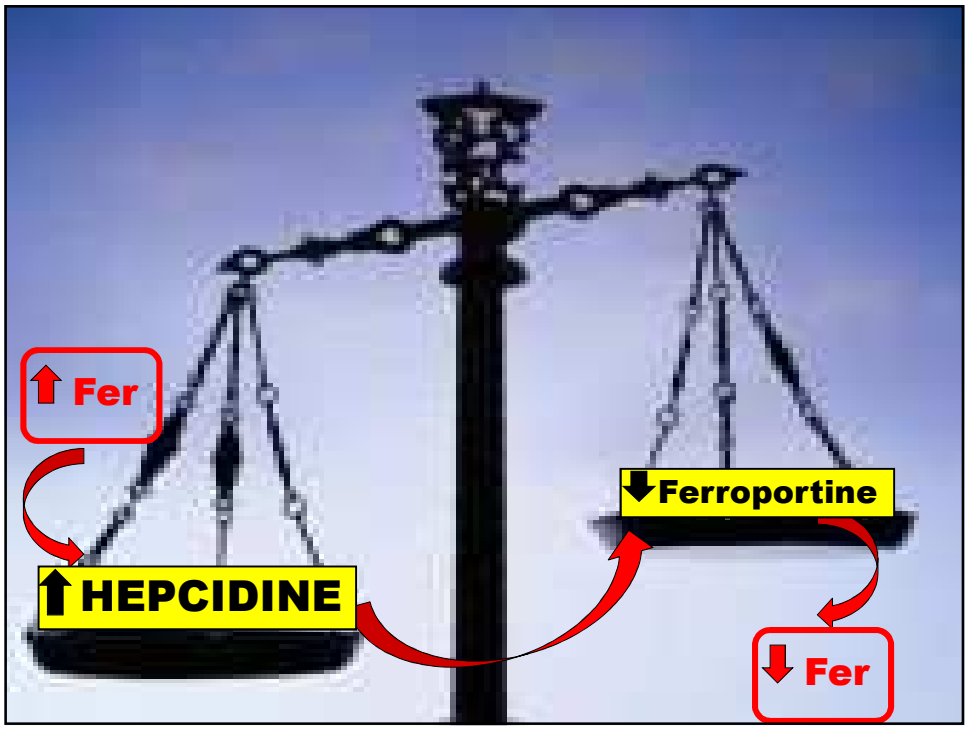

HEPCIDINE
Ferroportine

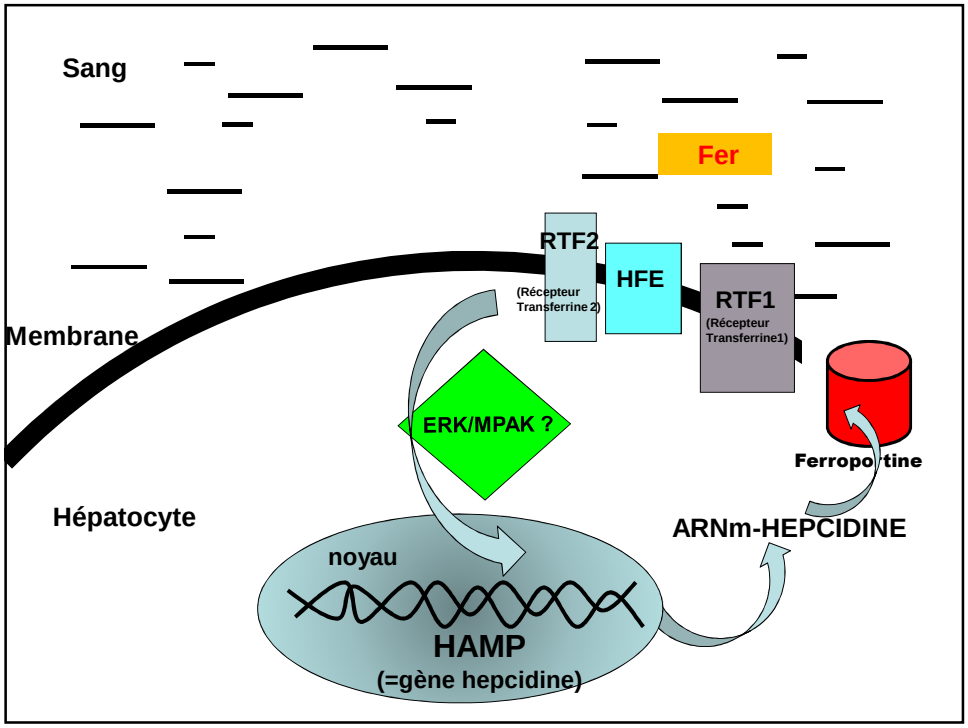

Hepcidine
FERROPORTINE

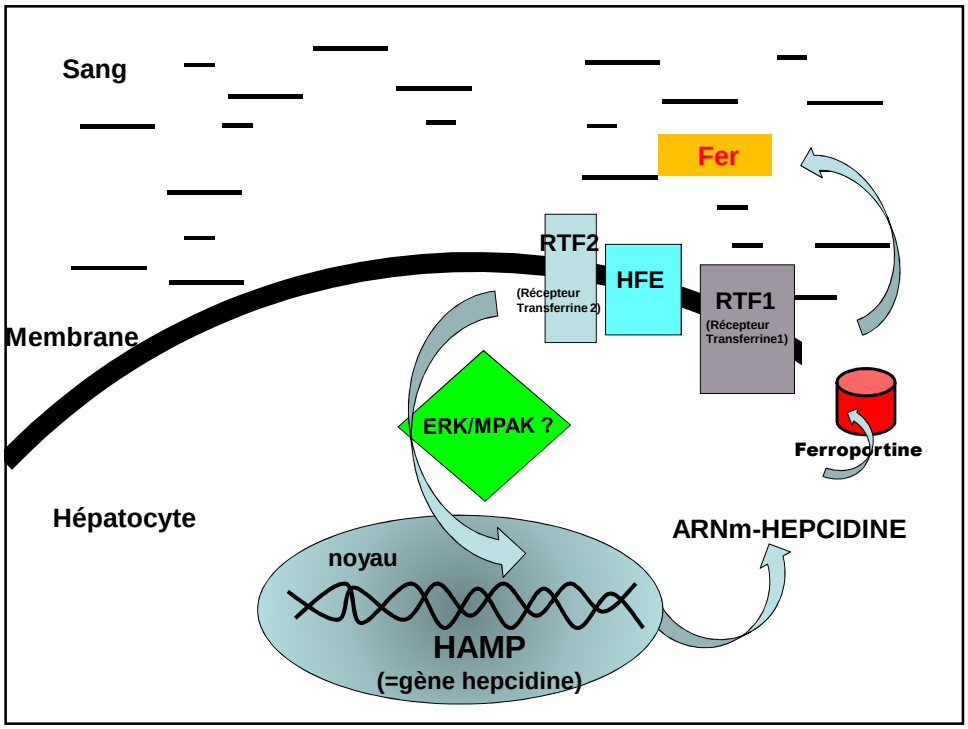

Fer
Hepcidine
FERROPORTINE
Fer


Hepcidine
Fe
portine
Ferroportine
Fe


Fe


Fer
HEPCIDINE
Ferroportine
Fer


Sang
Fer
RTF2
(Récepteur Transferrine 2)
HFE
RTF1
(Récepteur Transferrine1)
Membrane
ERK/MPAK ?
Ferroportine
Hépatocyte
ARNm-HEPCIDINE
noyau
HAMP
(=gène hepcidine)



Aspects physiologiques

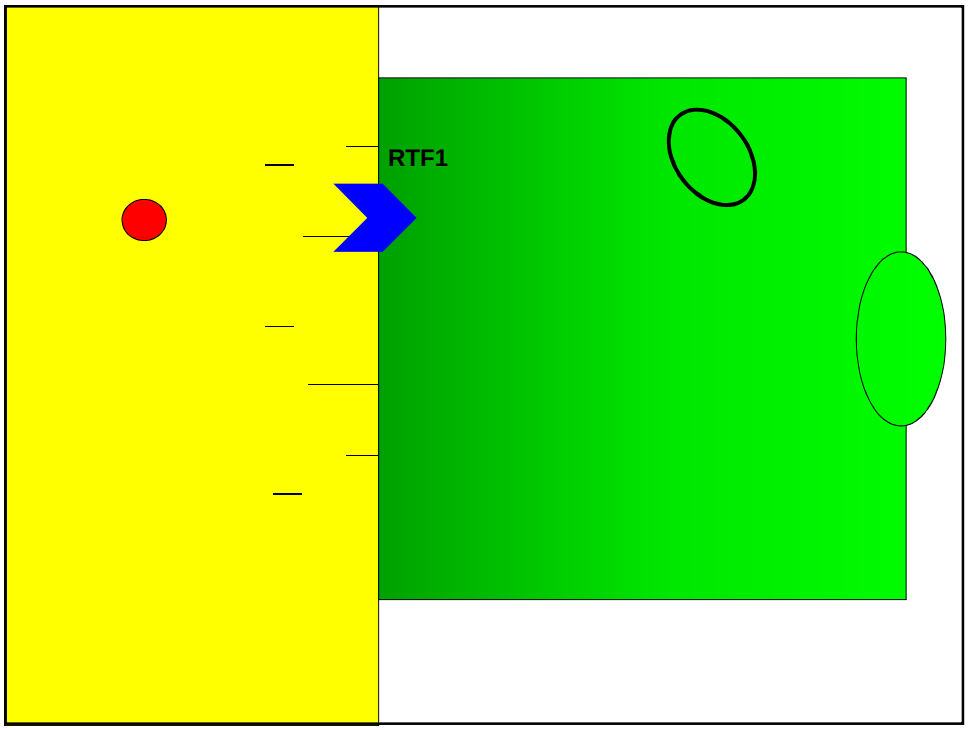
Régulation du fer

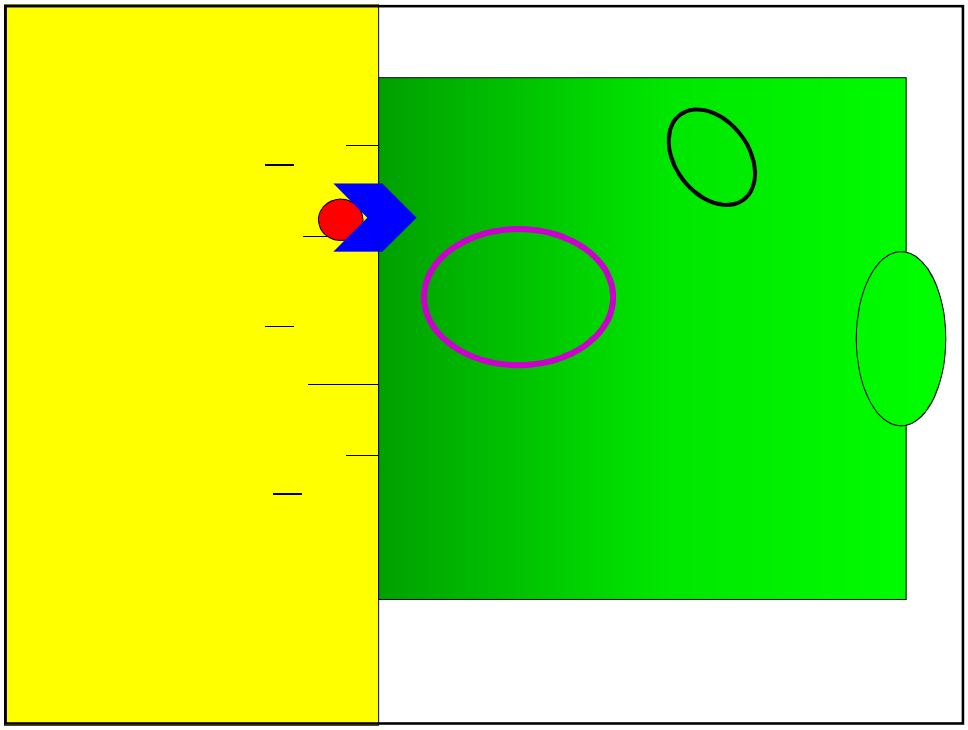
Régulation générale

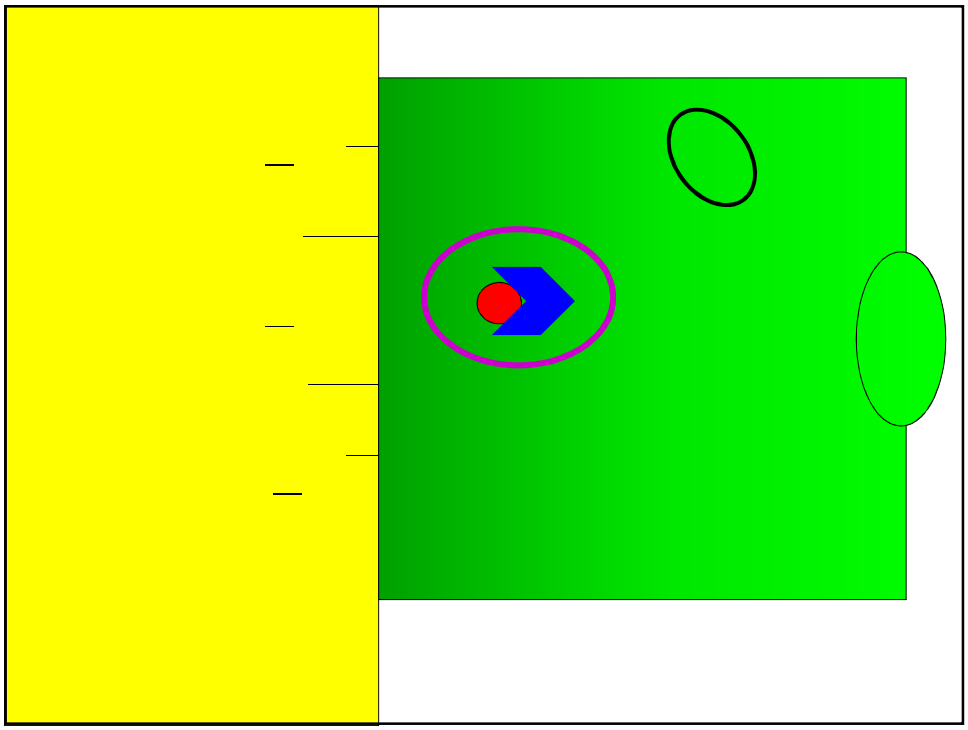
Régulation locale

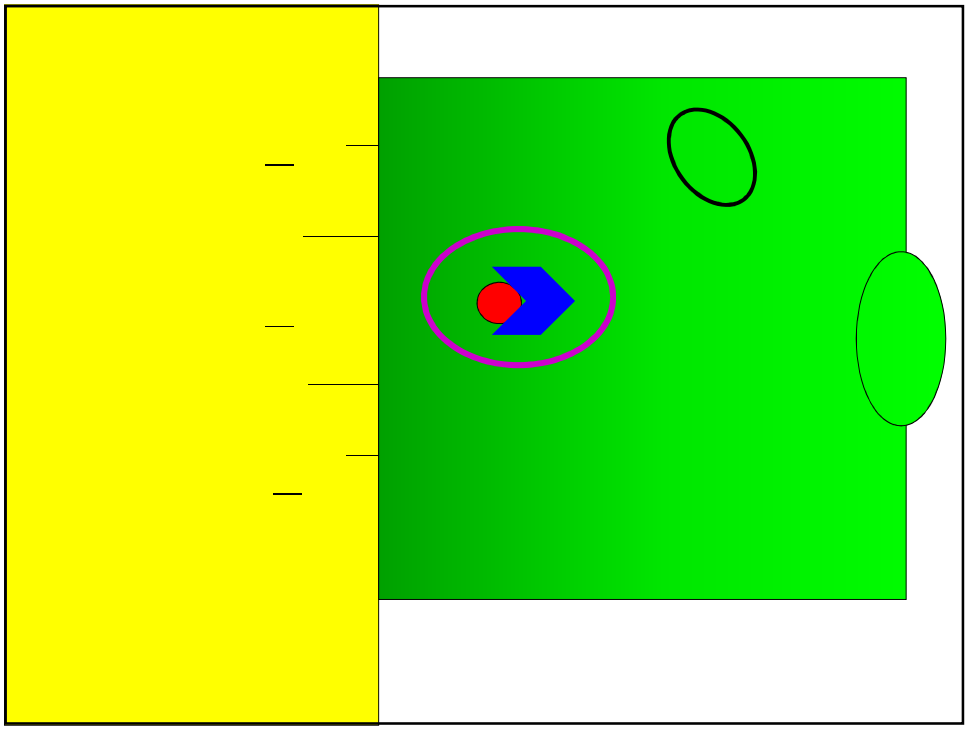
= Régulation «systémique»

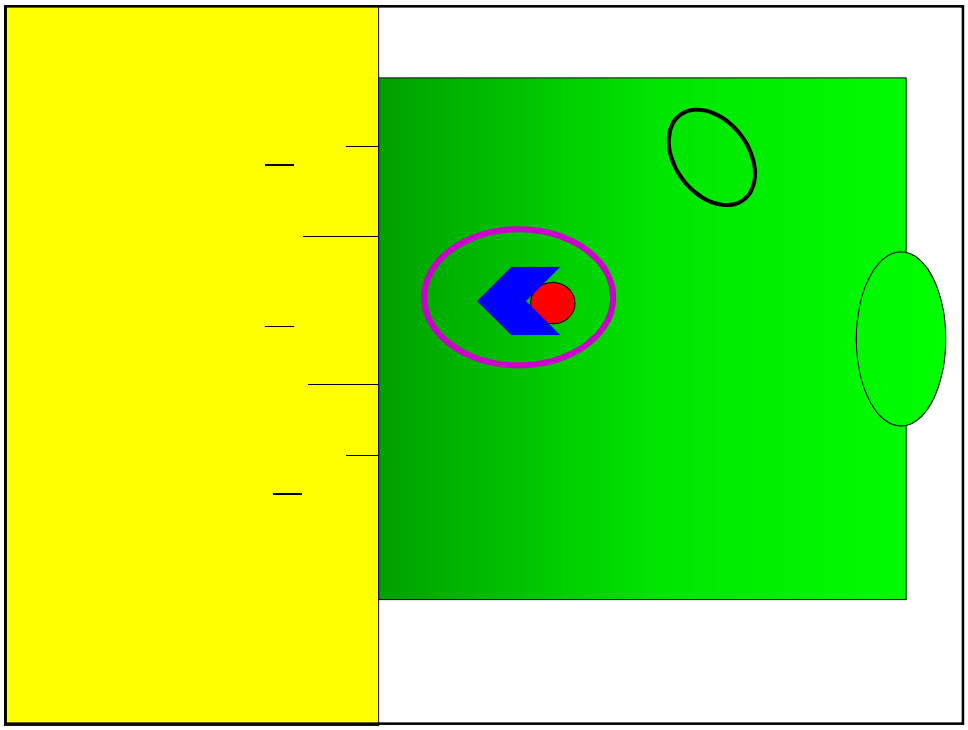
= Régulation «intracellulaire»

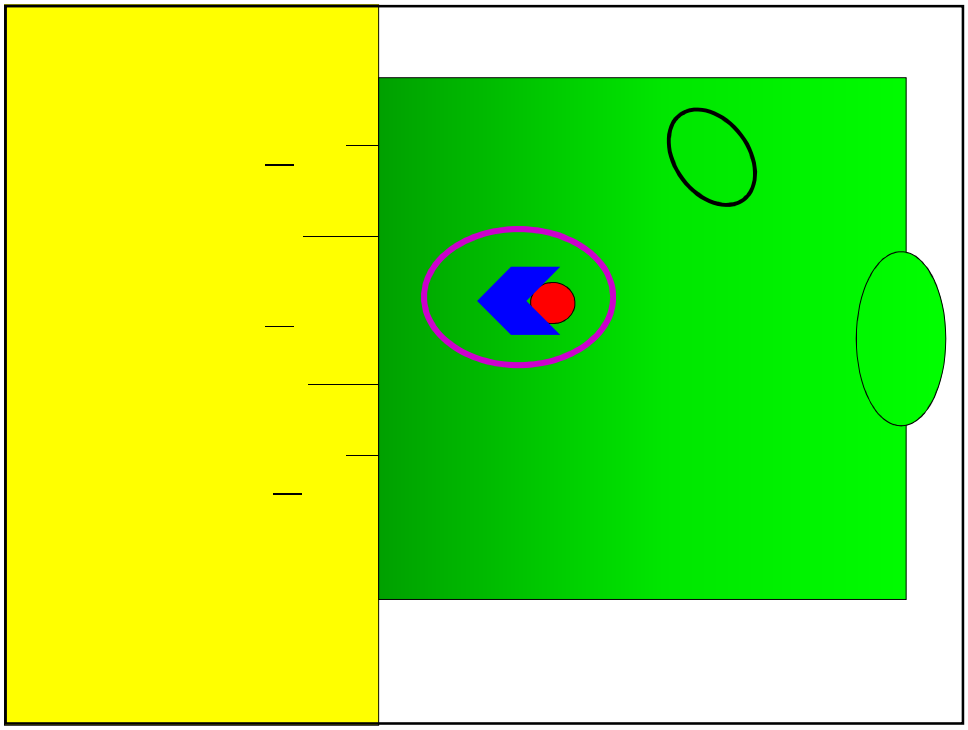

RTF1

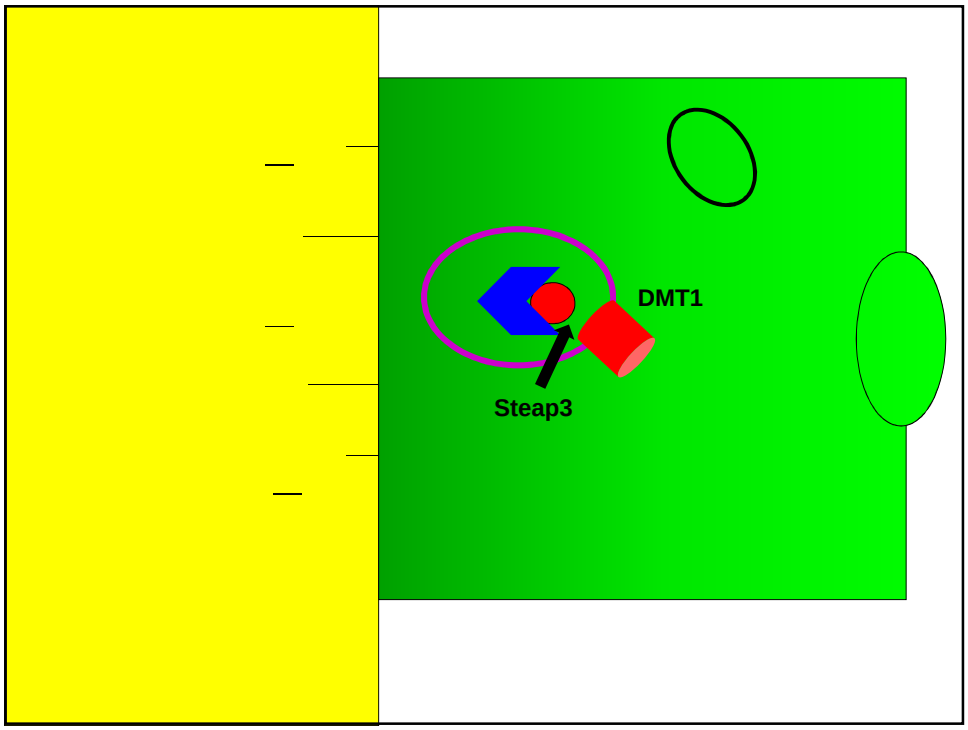


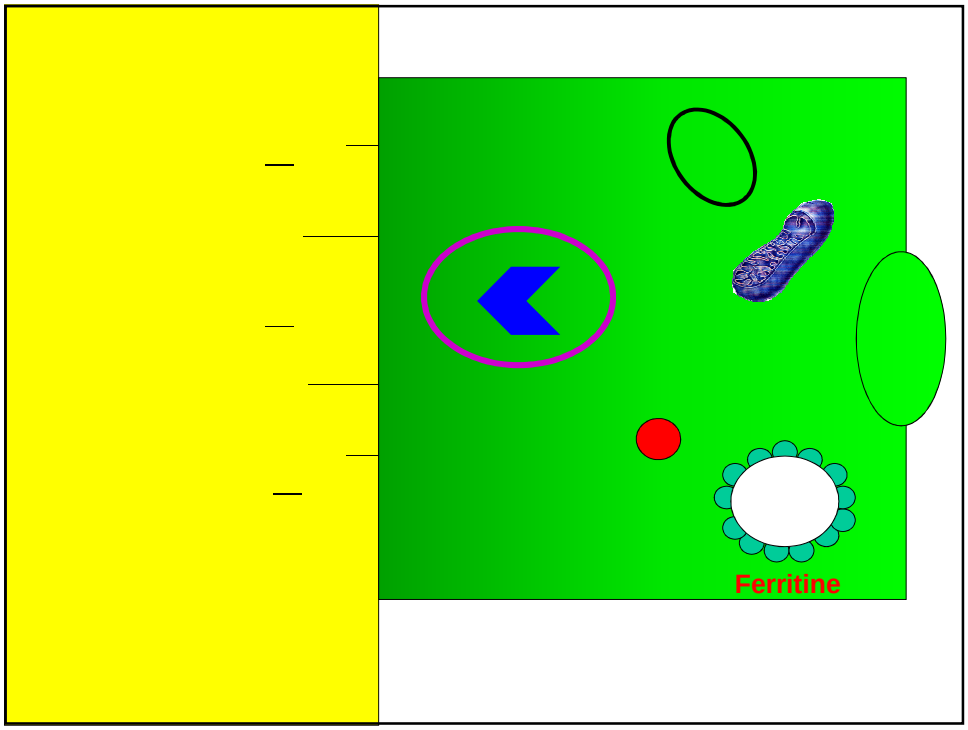


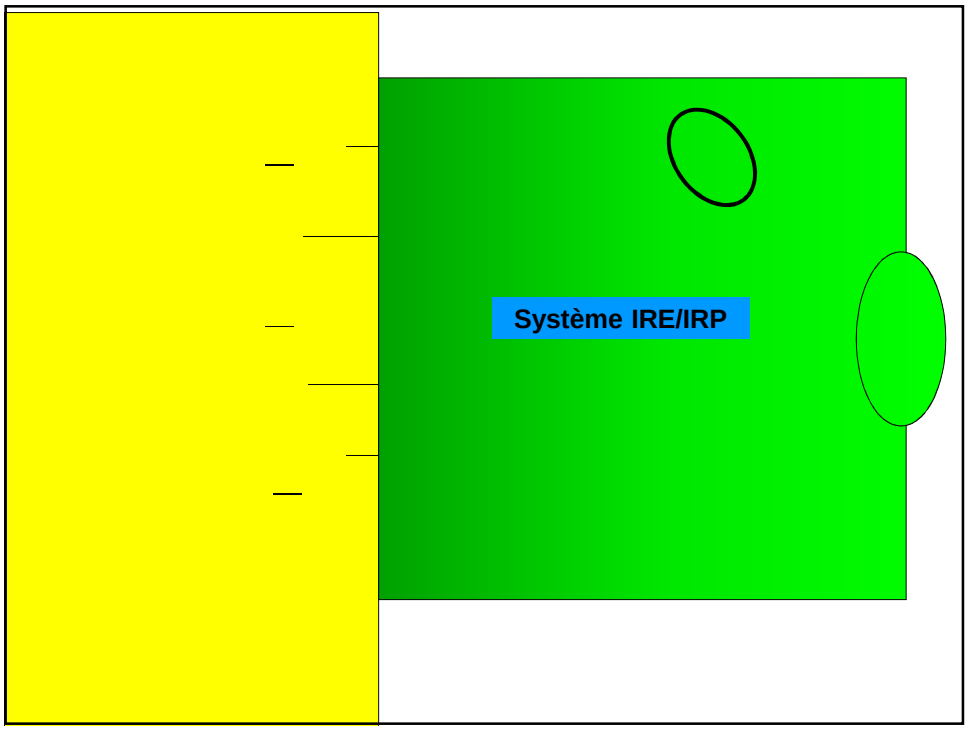


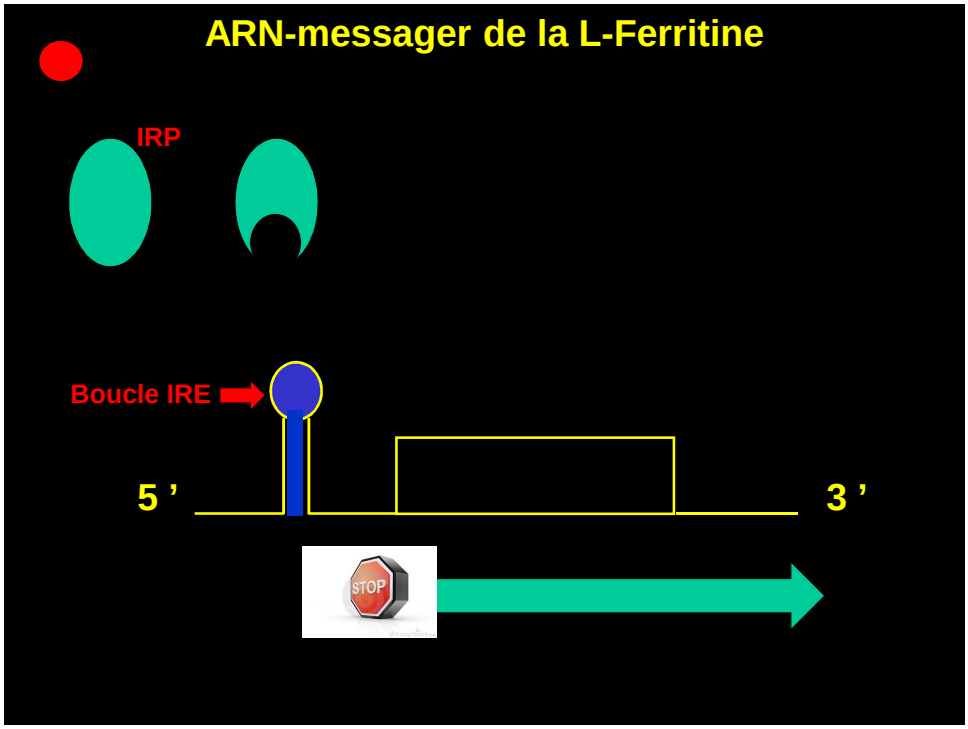


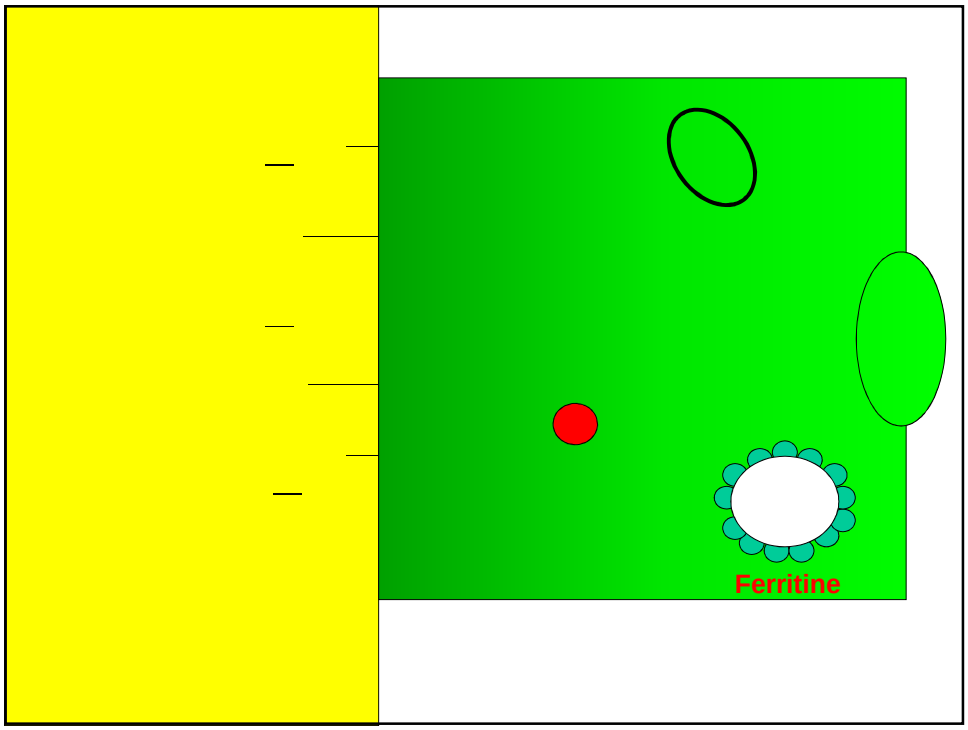


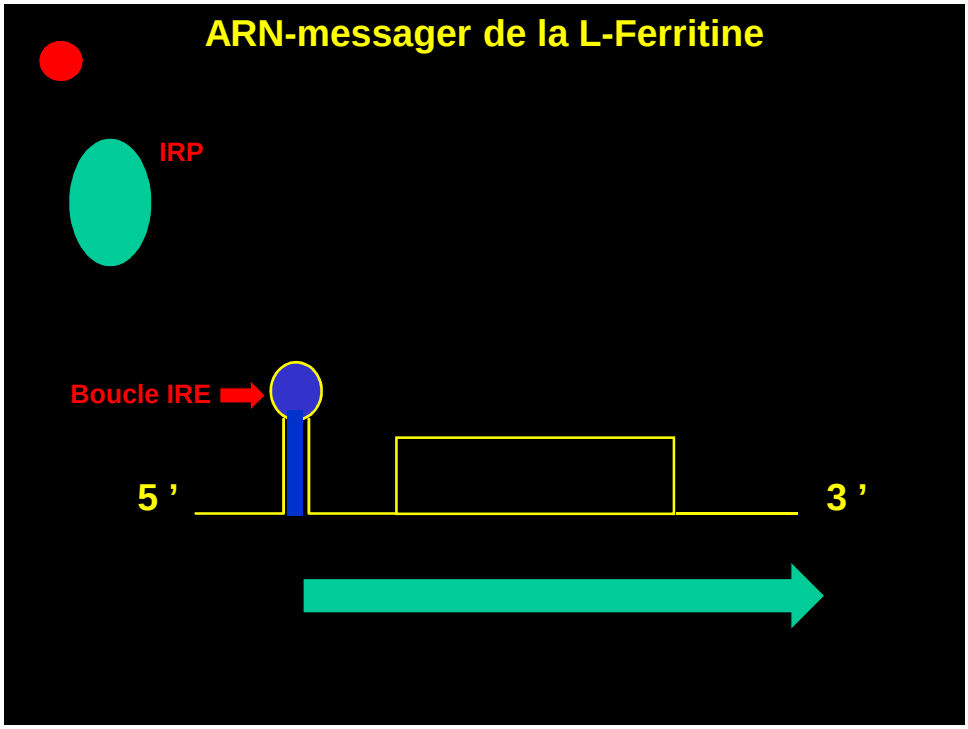

DMT1
Steap3

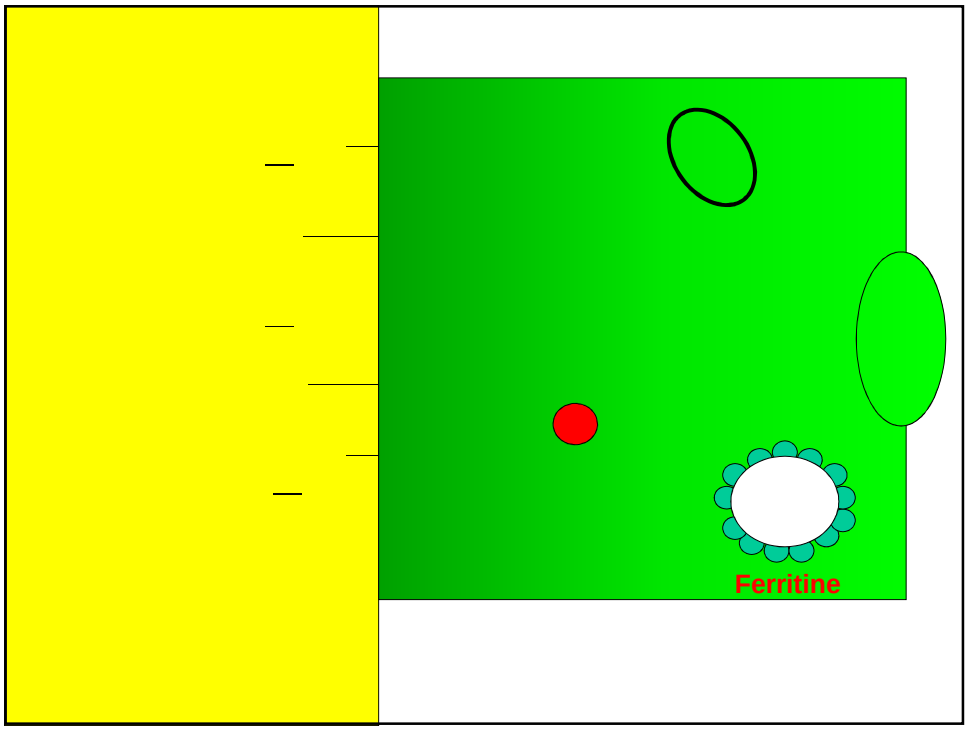

Ferritine

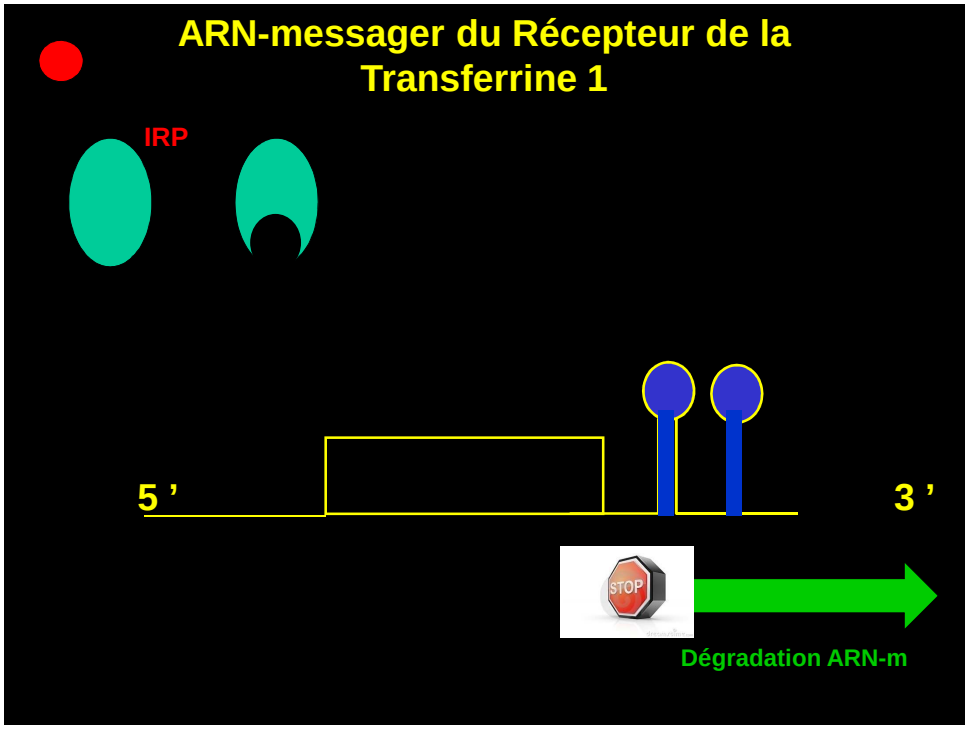

Système IRE/IRP

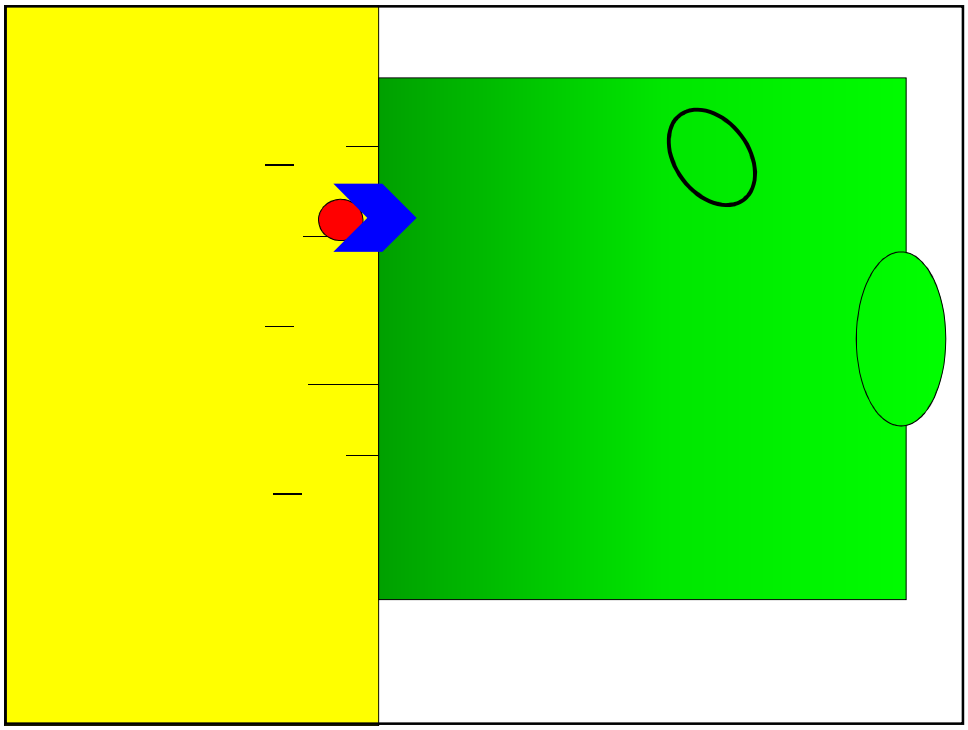

ARN-messager de la L-Ferritine
IRP
Boucle IRE
5 ’
3 ’
STOP


Ferritine


ARN-messager de la L-Ferritine
IRP
Boucle IRE
5 ’
3 ’


Ferritine

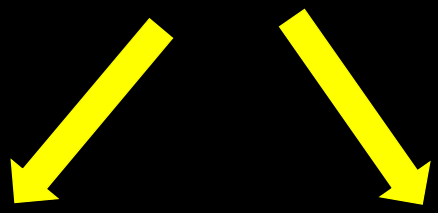

ARN-messager du Récepteur de la Transferrine 1
IRP
5 ’
3 ’
STOP
Dégradation ARN-m



Aspects physiologiques

Aspects physio-pathologiques

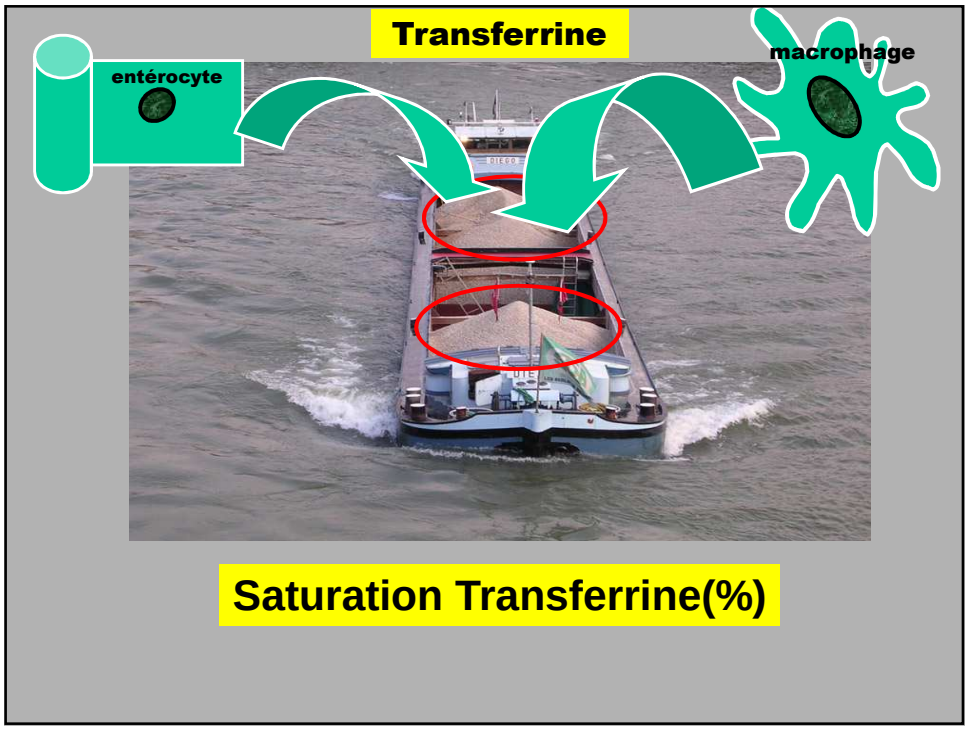
Aspects physio-pathologiques

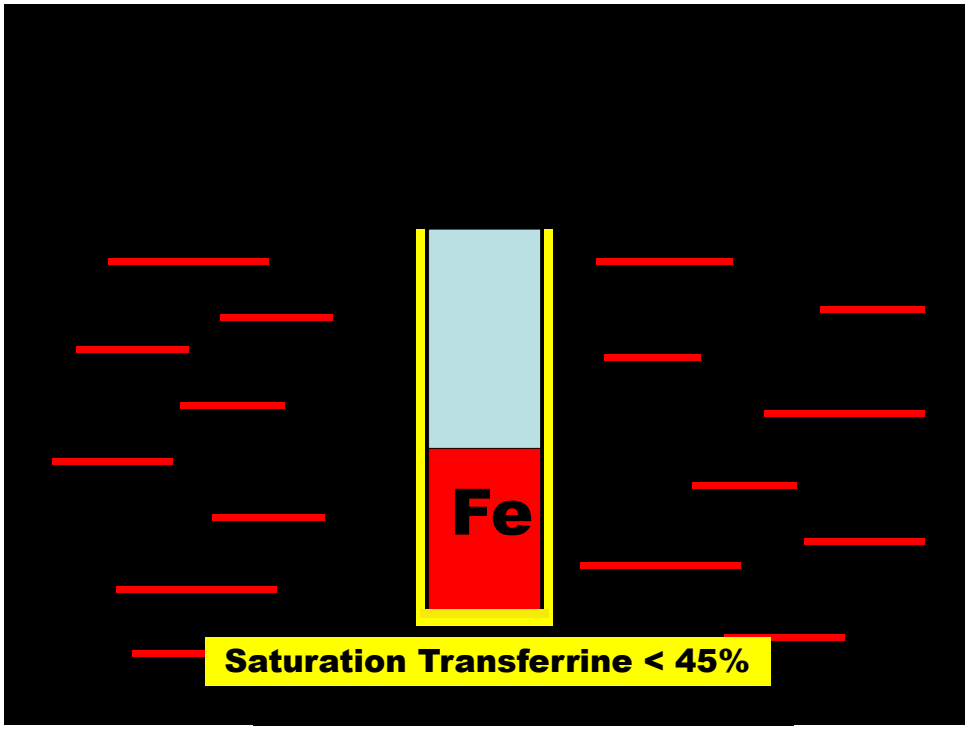


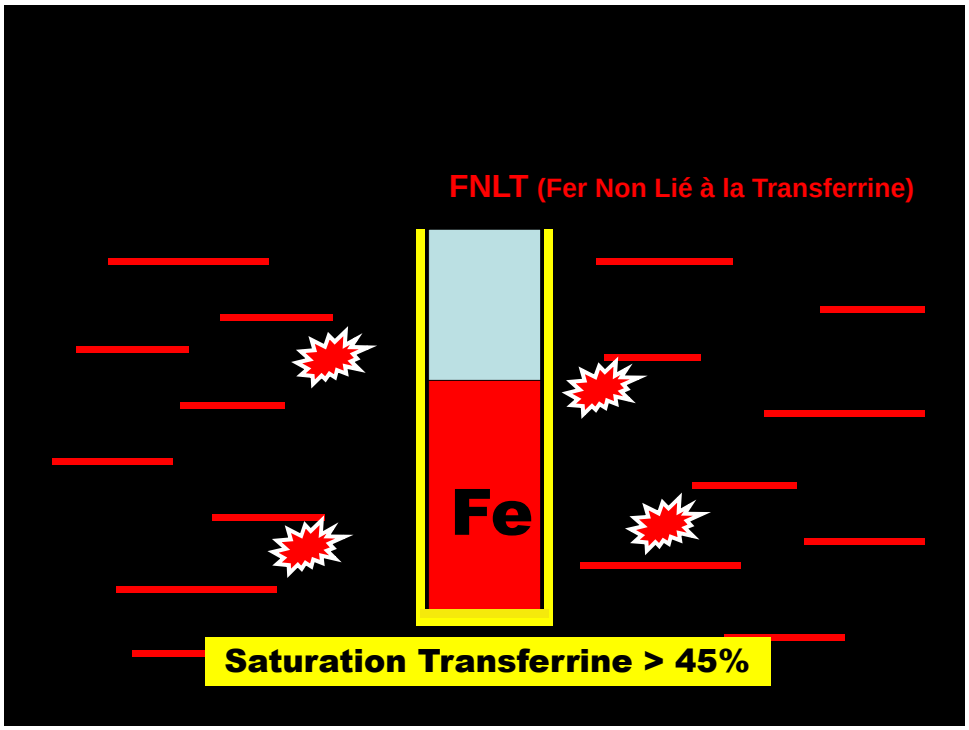
Toxicité du fer

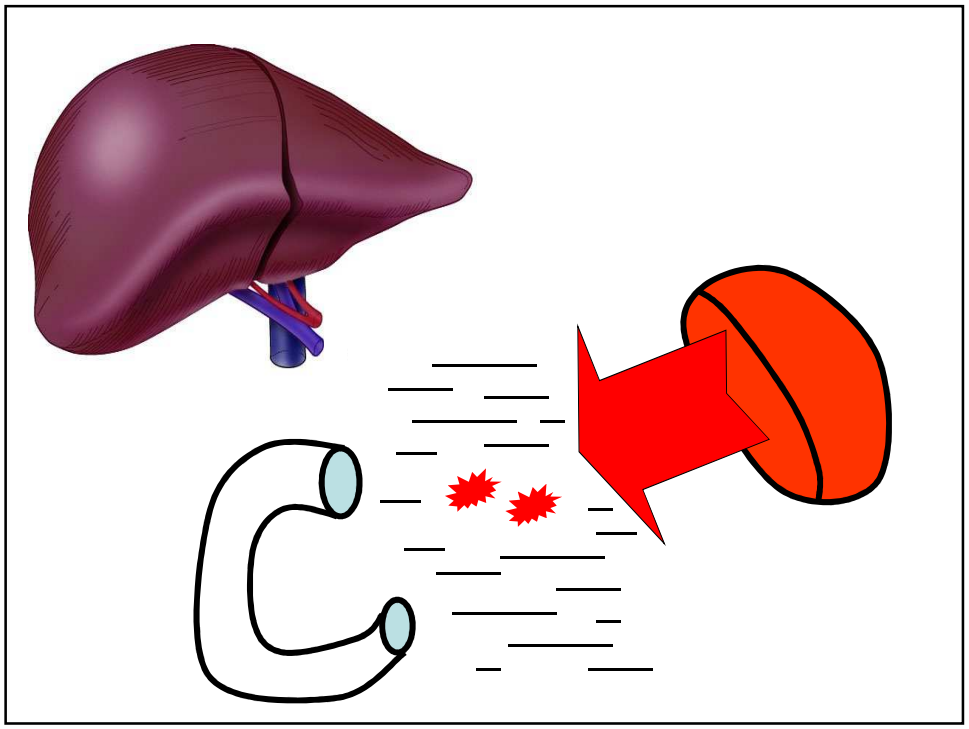
Pathologies du fer

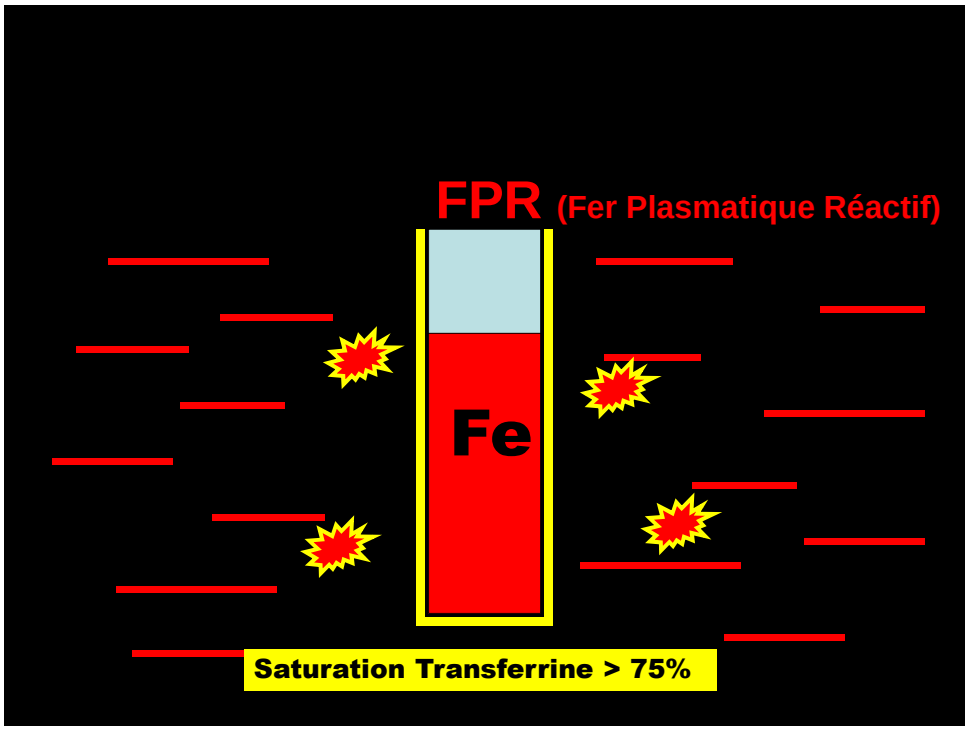
FER NON LIE A LA TRANSFERRINE (FNLT)

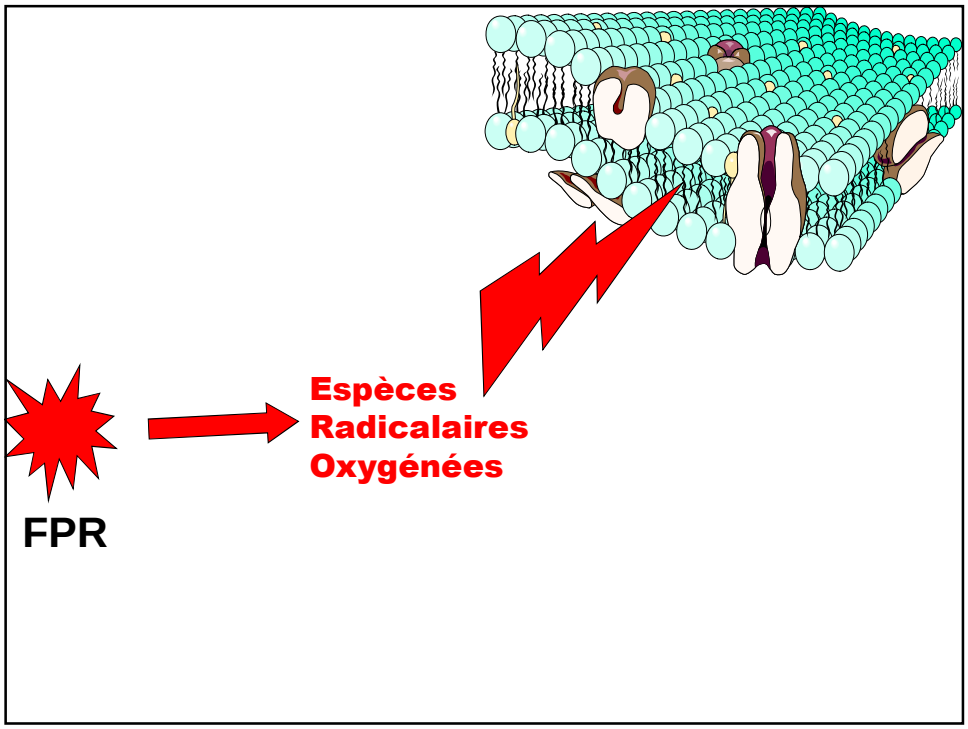

Transferrine
entérocyte
macrophage
Saturation Transferrine(%)

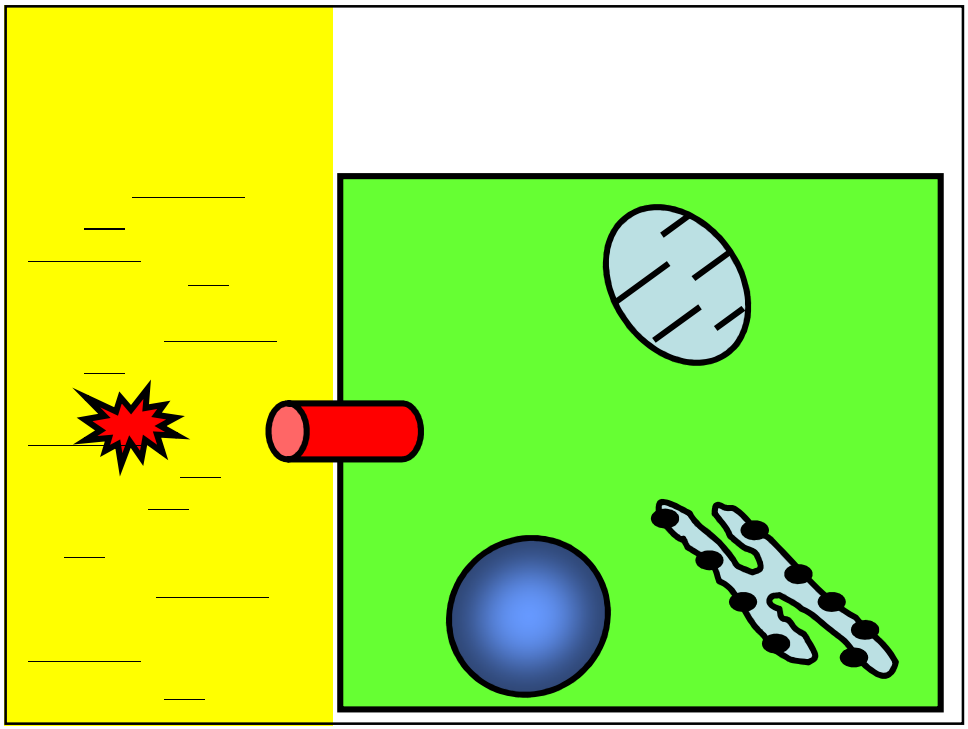

Fe
Saturation Transferrine < 45%

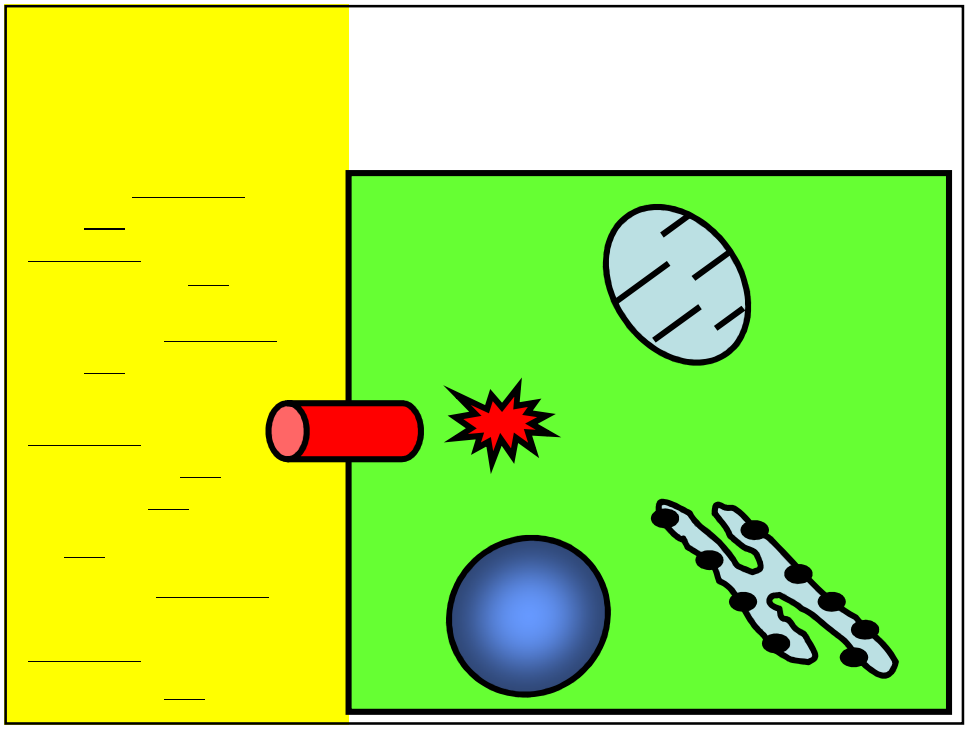

FNLT (Fer Non Lié à la Transferrine)
Fe
Saturation Transferrine > 45%



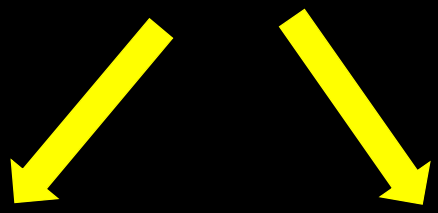

FPR (Fer Plasmatique Réactif)
Fe
Saturation Transferrine > 75%


Espèces
Radicalaires
Oxygénées
FPR





Aspects physio-pathologiques



Toxicité du fer

Pathologies du fer

EXCES EN HEPCIDINE

DEFICITS EN HEPCIDINE

Acquis

ou

Génétiques

EXCES EN HEPCIDINE

- **Causes acquises**
- **Cause génétique**

DEFICITS EN HEPCIDINE

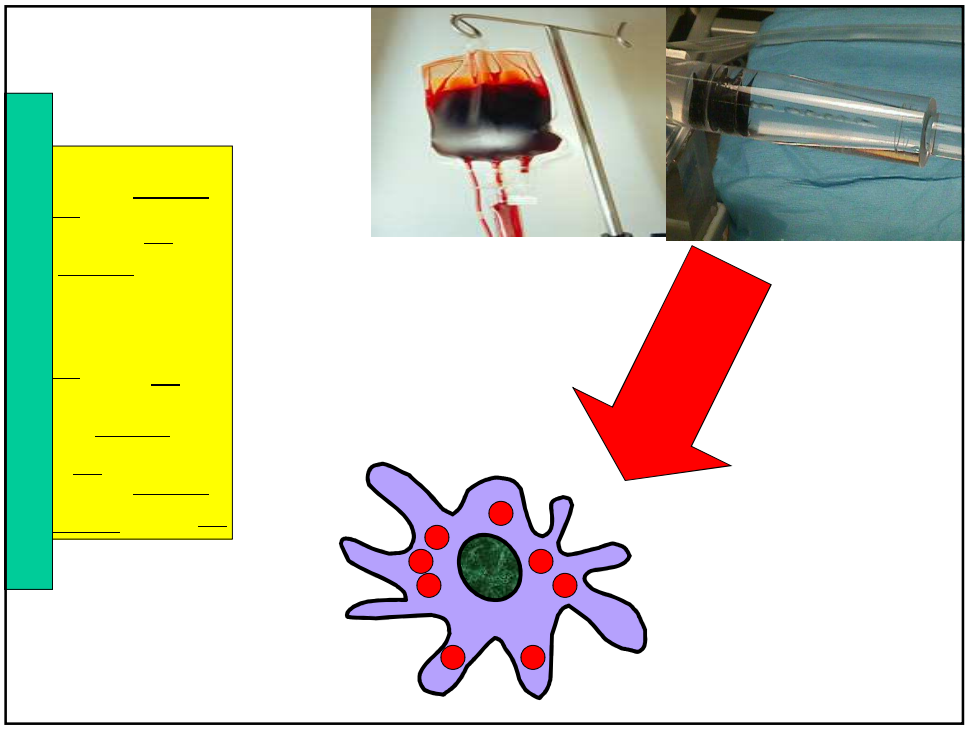
Surcharges acquises en fer

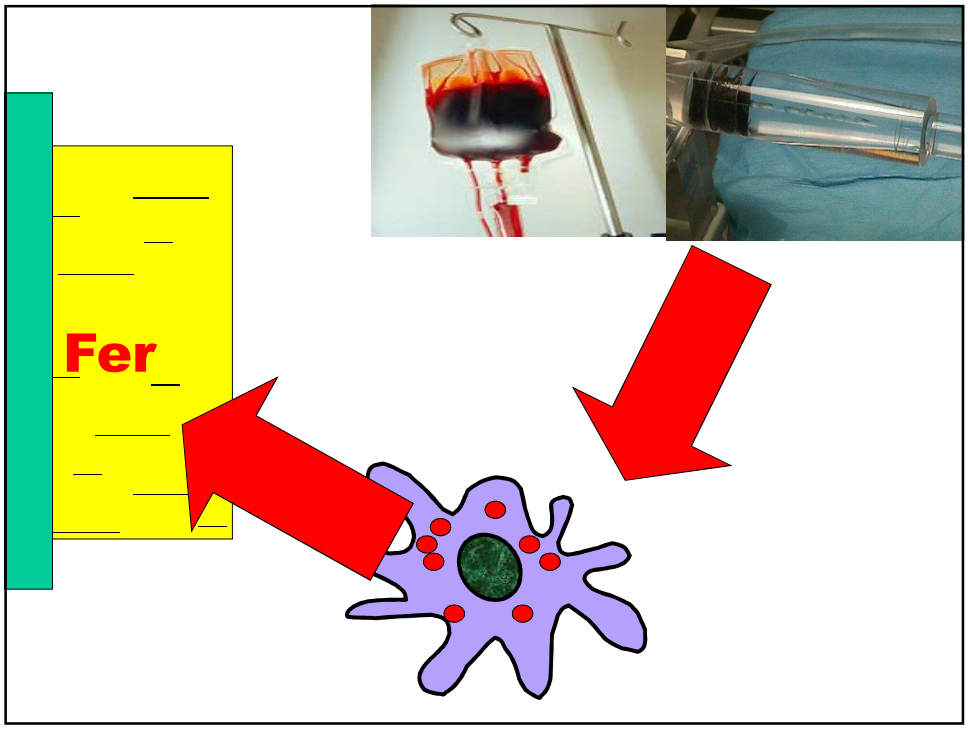
Transfusions

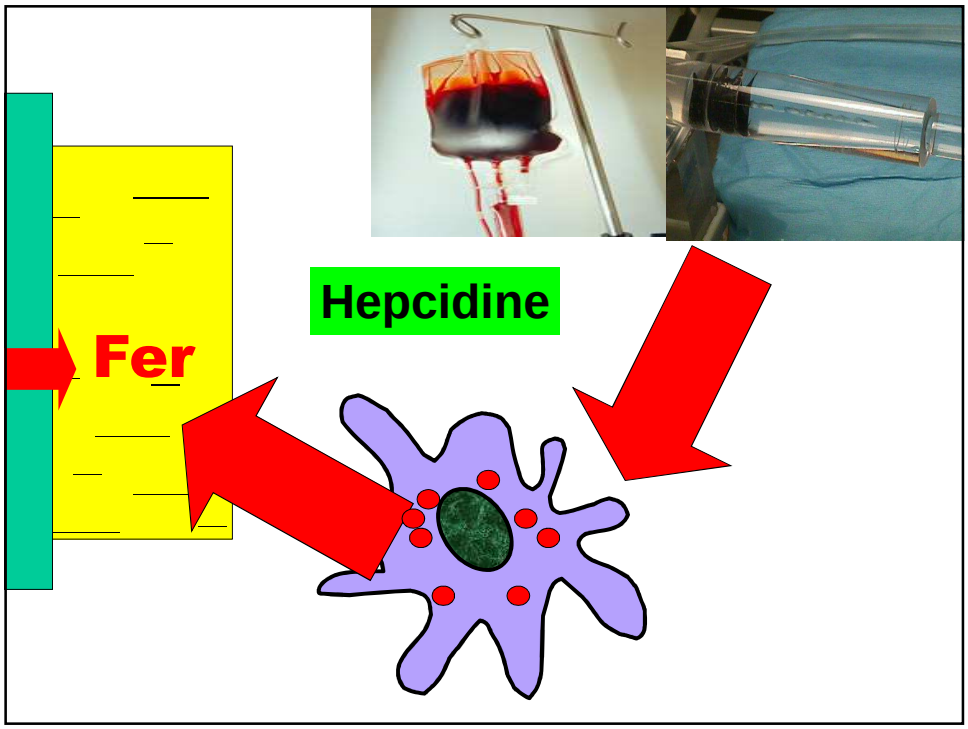
Fer intraveineux

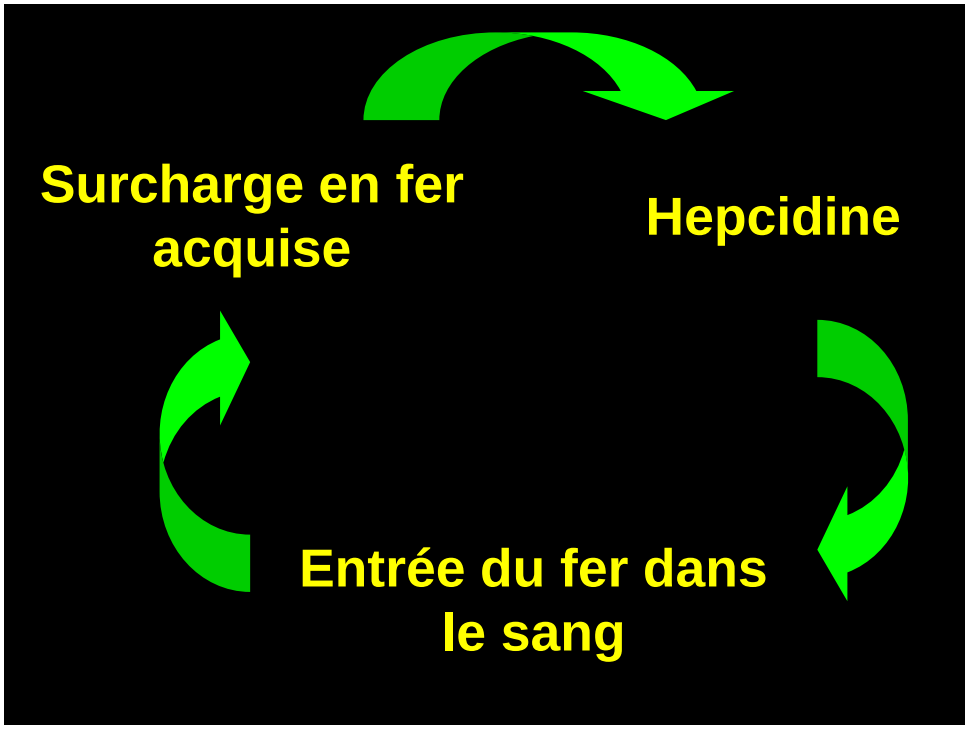
Apport parentéral

Surcharge en fer




Fer


Hepcidine
Fer

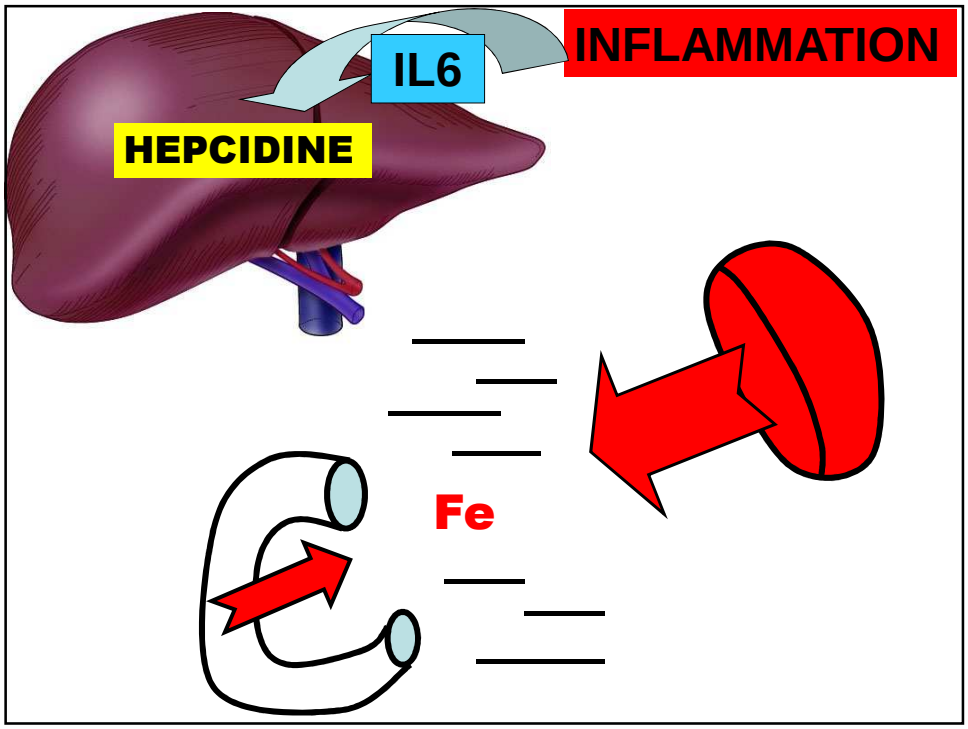

Surcharge en fer acquise
Hepcidine
Entrée du fer dans le sang

EXCES EN HEPCIDINE

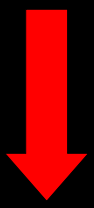
- Causes acquises
- Cause génétique

DEFICITS EN HEPCIDINE

INFLAMMATION


INFLAMMATION
IL6
HEPCIDINE
Fe

INFLAMMATION



ANEMIE

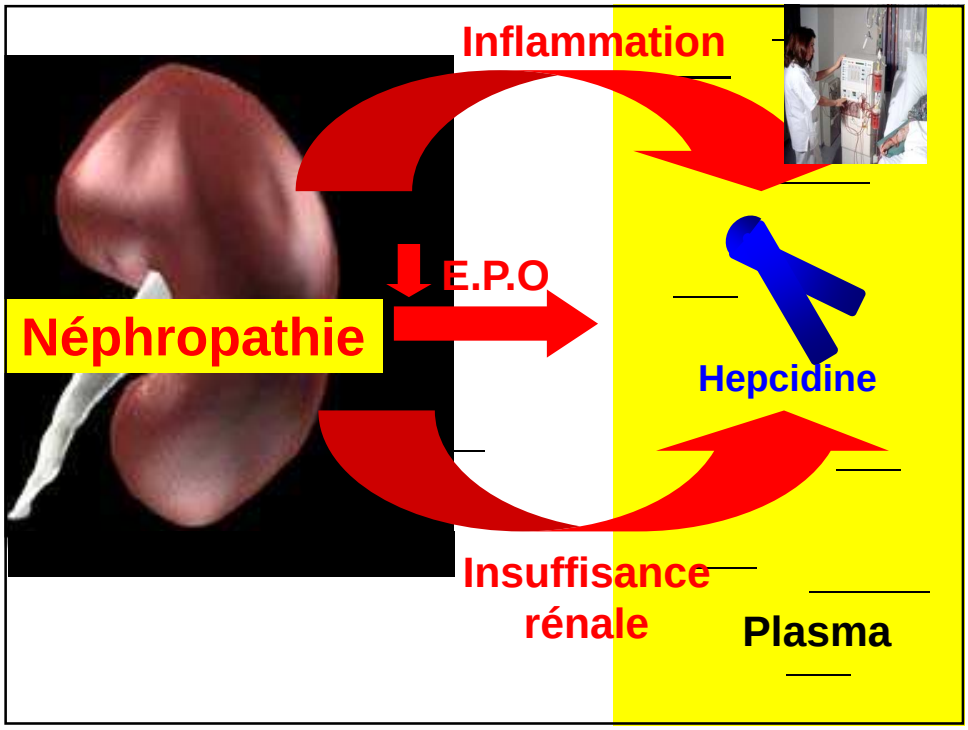
« Anémie des maladies chroniques »

EXCES EN HEPCIDINE

- **Causes acquises**
- **Cause génétique**

DEFICITS EN HEPCIDINE

NEPHROPATHIE CHRONIQUE



EXCES EN HEPCIDINE

- **Causes acquises**
- **Cause génétique**

DEFICITS EN HEPCIDINE

Anémie ferriprive

Anémie ferriprive, majeure,

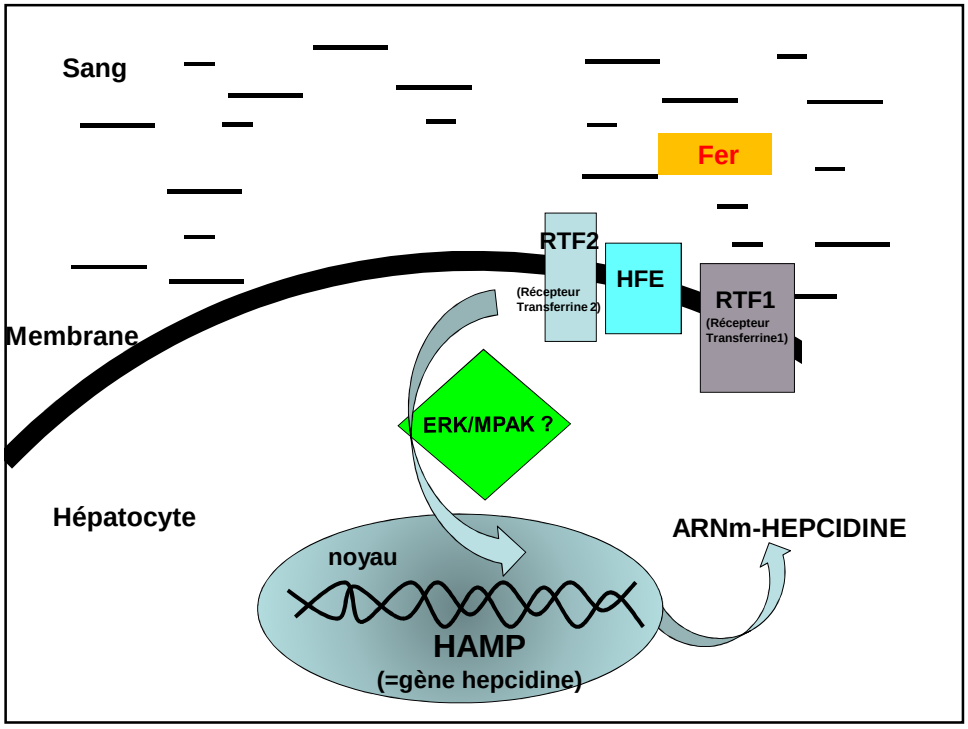
Anémie ferriprive, majeure, chronique

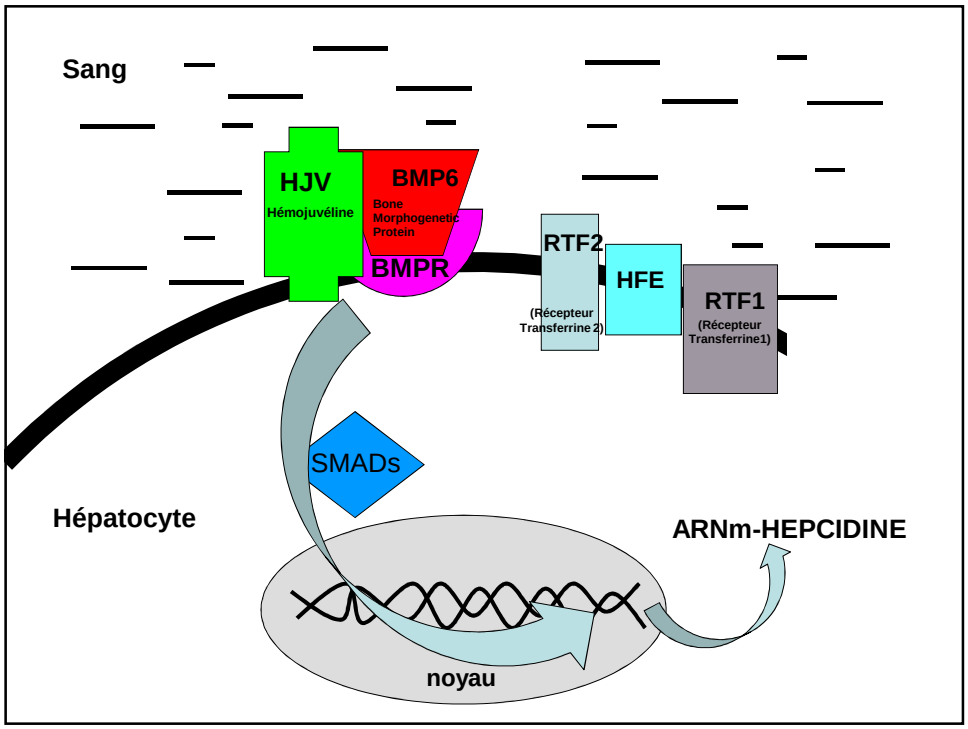
Anémie ferriprive, majeure, chronique, inexpliquée

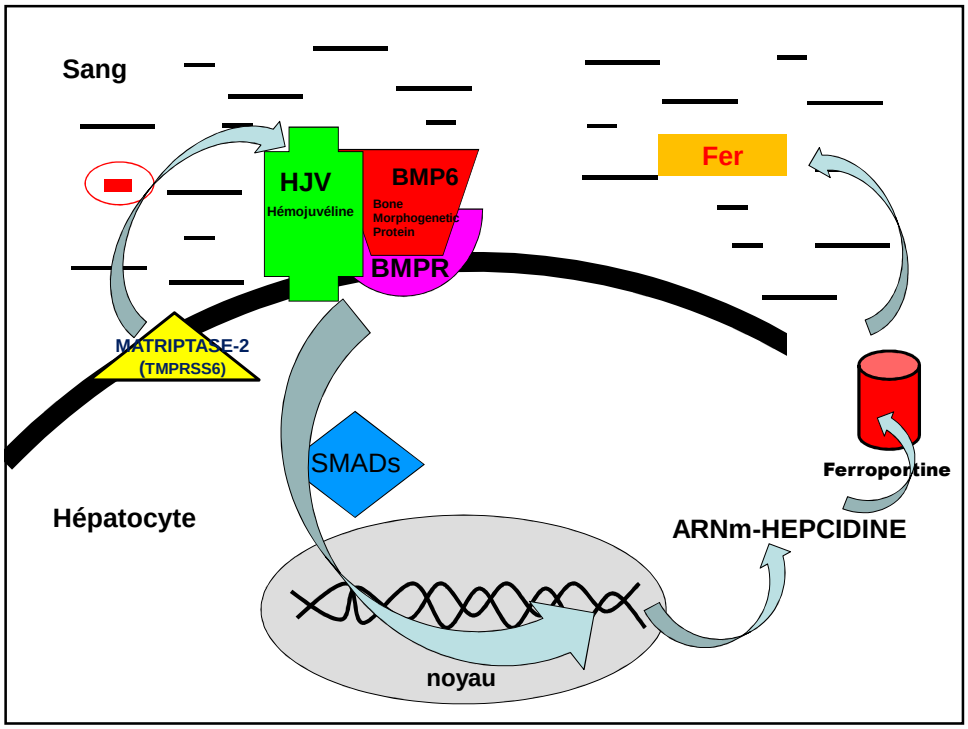
Anémie ferriprive, majeure, chronique, inexpliquée, réfractaire

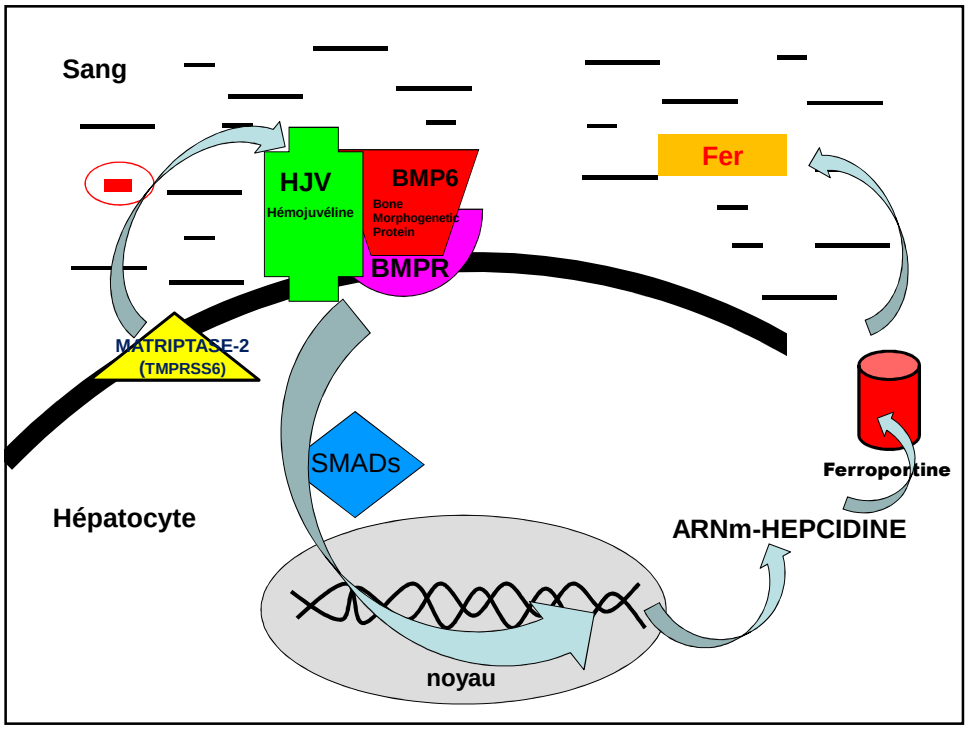
IRIDA

Iron Refractory Iron Deficiency Anemia




Sang
HJV
Hémojuvéline
BMP6
Bone Morphogenetic Protein
BMPR
RTF2
(Récepteur Transferrine 2)
HFE
RTF1
(Récepteur Transferrine1)
SMADs
Hépatocyte
ARNm-HEPCIDINE
noyau


Sang
HJV
Hémojuvéline
BMP6
Bone Morphogenetic Protein
BMPR
Fer
MATRIPTASE-2
(TMPRSS6)
SMADs
Ferroportine
Hépatocyte
ARNm-HEPCIDINE
noyau



EXCES EN HEPCIDINE

- Causes acquises
- Cause génétique

DEFICITS EN HEPCIDINE

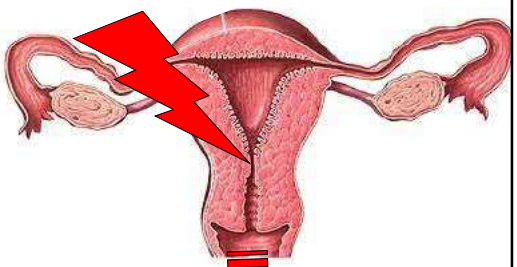
- Causes acquises
- Causes génétiques

Déficit en fer quantitatif
(=baisse des réserves en fer)

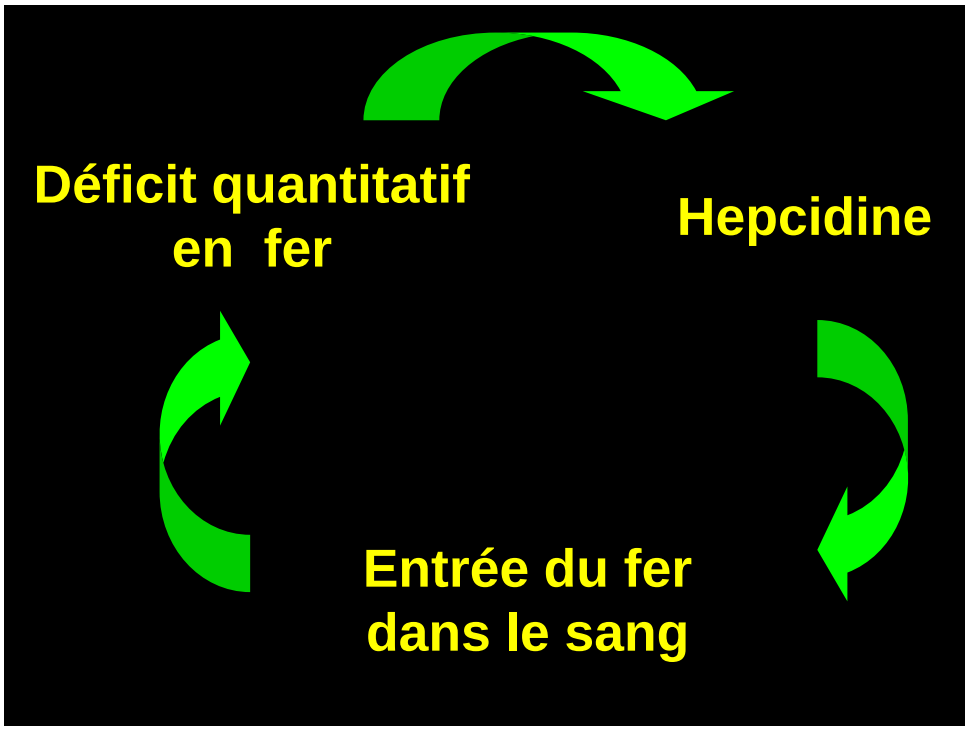
Carence d'apport

Pertes

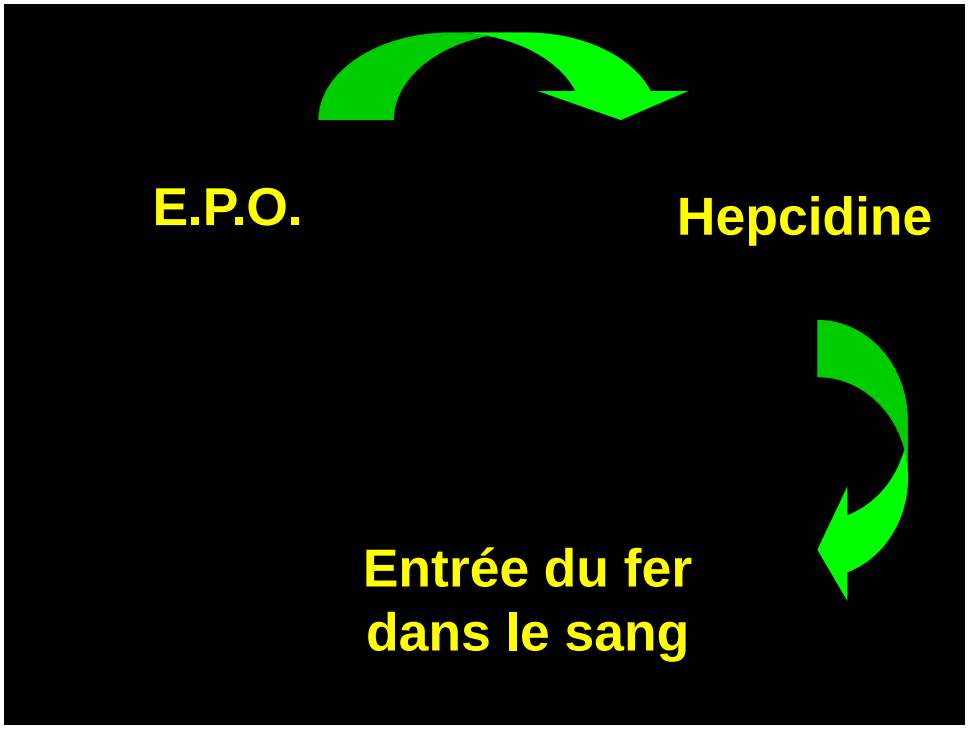
Pertes digestives

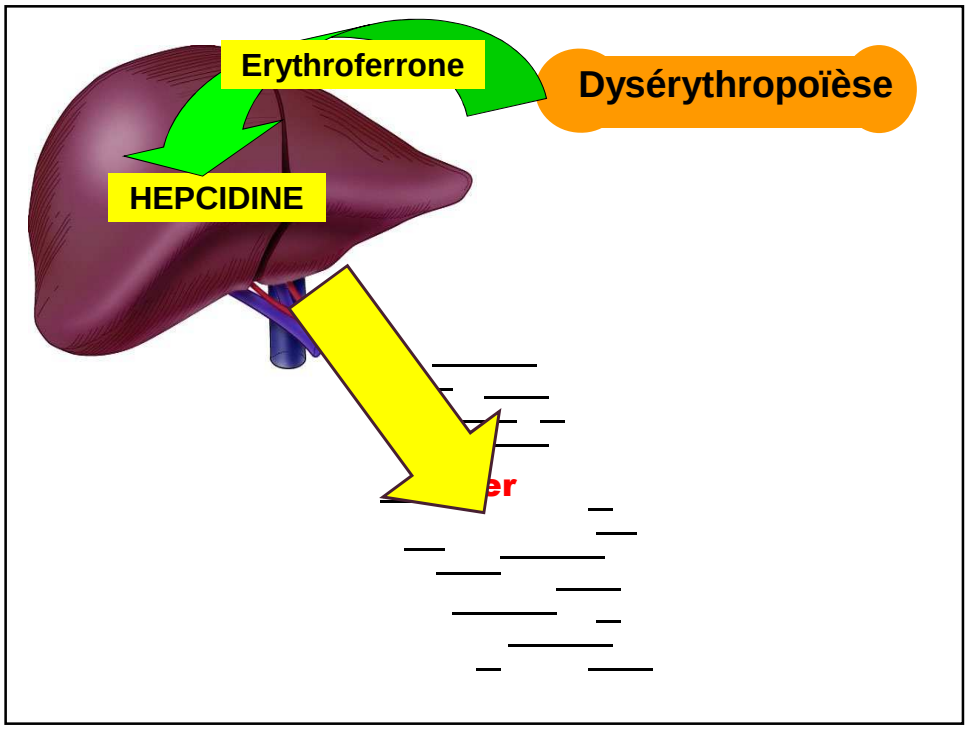


Pertes gynécologiques


Déficit quantitatif
en fer
Hepcidine
Entrée du fer
dans le sang


EPO


E.P.O.
Hepcidine
Entrée du fer
dans le sang

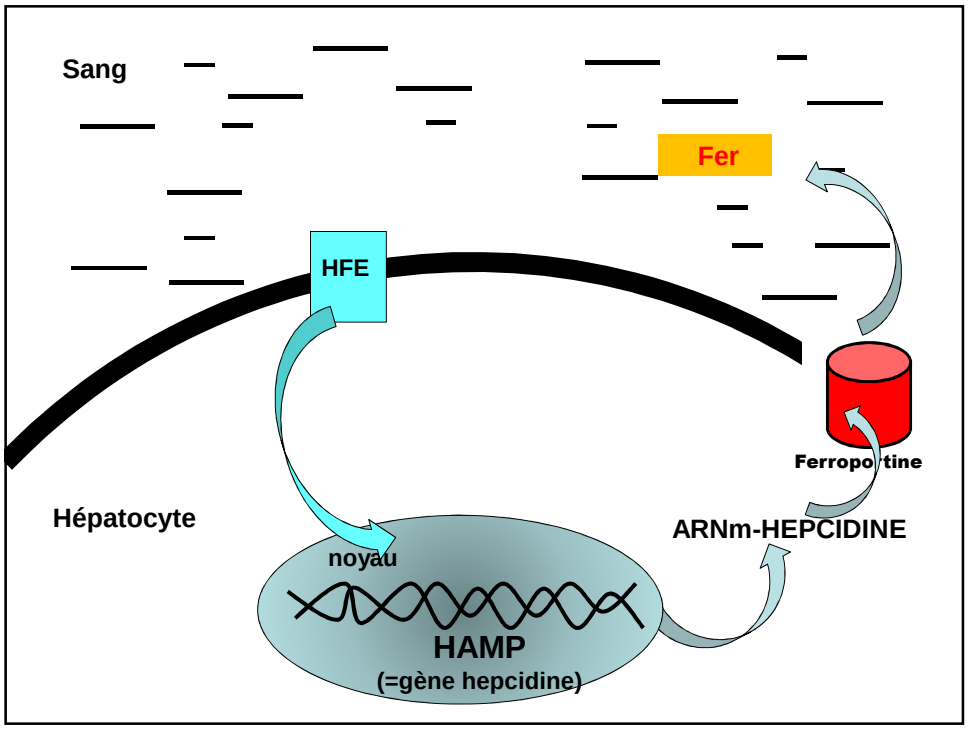


EXCES EN HEPCIDINE

- Causes acquises
- Cause génétique

DEFICITS EN HEPCIDINE

- Causes acquises
- Causes génétiques…


Sang
Fer
HFE
Ferroportine
Hépatocyte
ARNm-HEPCIDINE
noyau
HAMP
(=gène hepcidine)