



National reference centre for rare  
genetic iron overload diseases

Pontchaillou University Hospital

Rennes (France)

# Haemochromatosis: A changing world

Pierre Brissot

Ulm

April, 23 2015







**HFE**

**HFE-related Haemochromatosis**

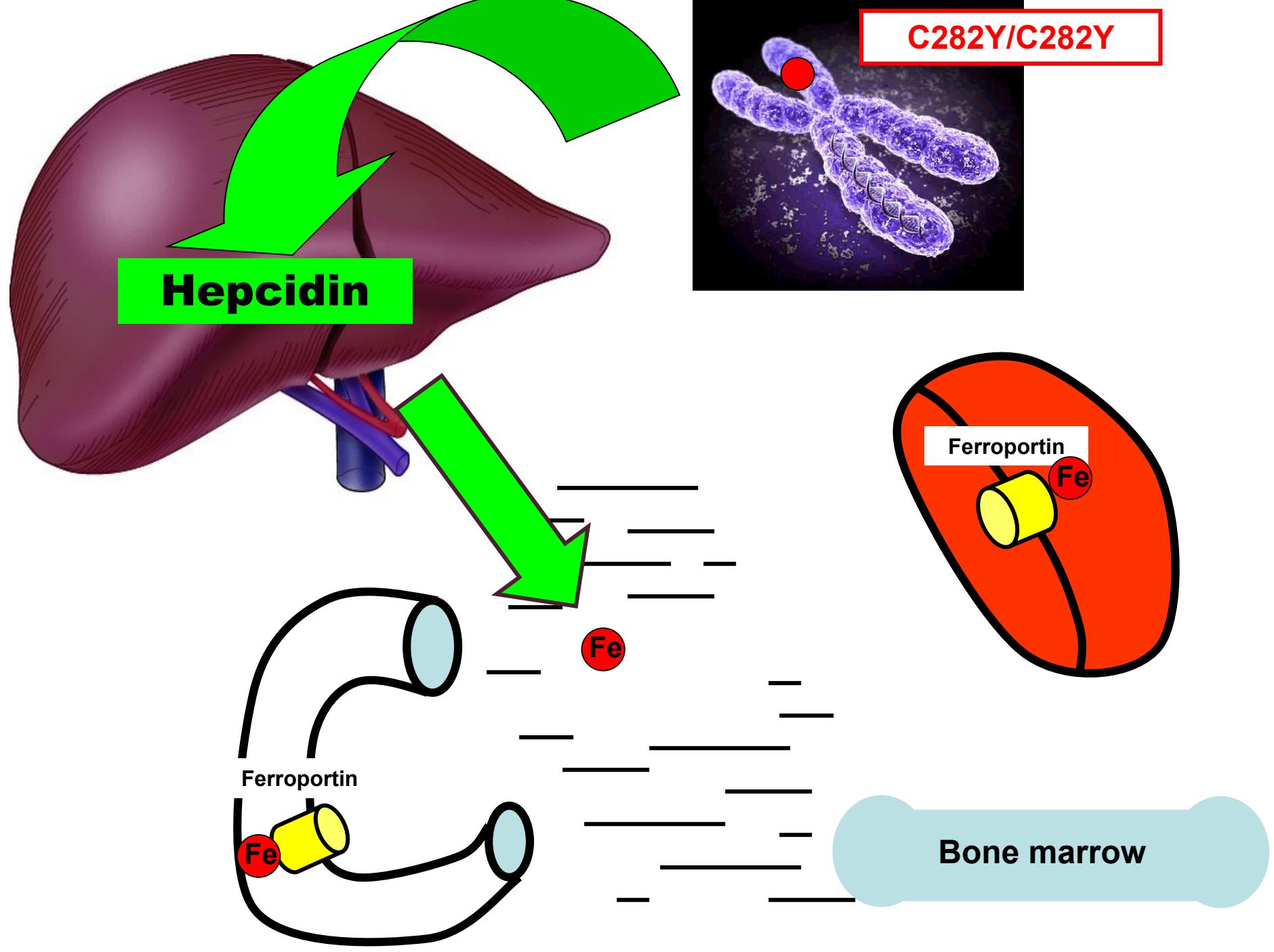
**C282Y/C282Y**

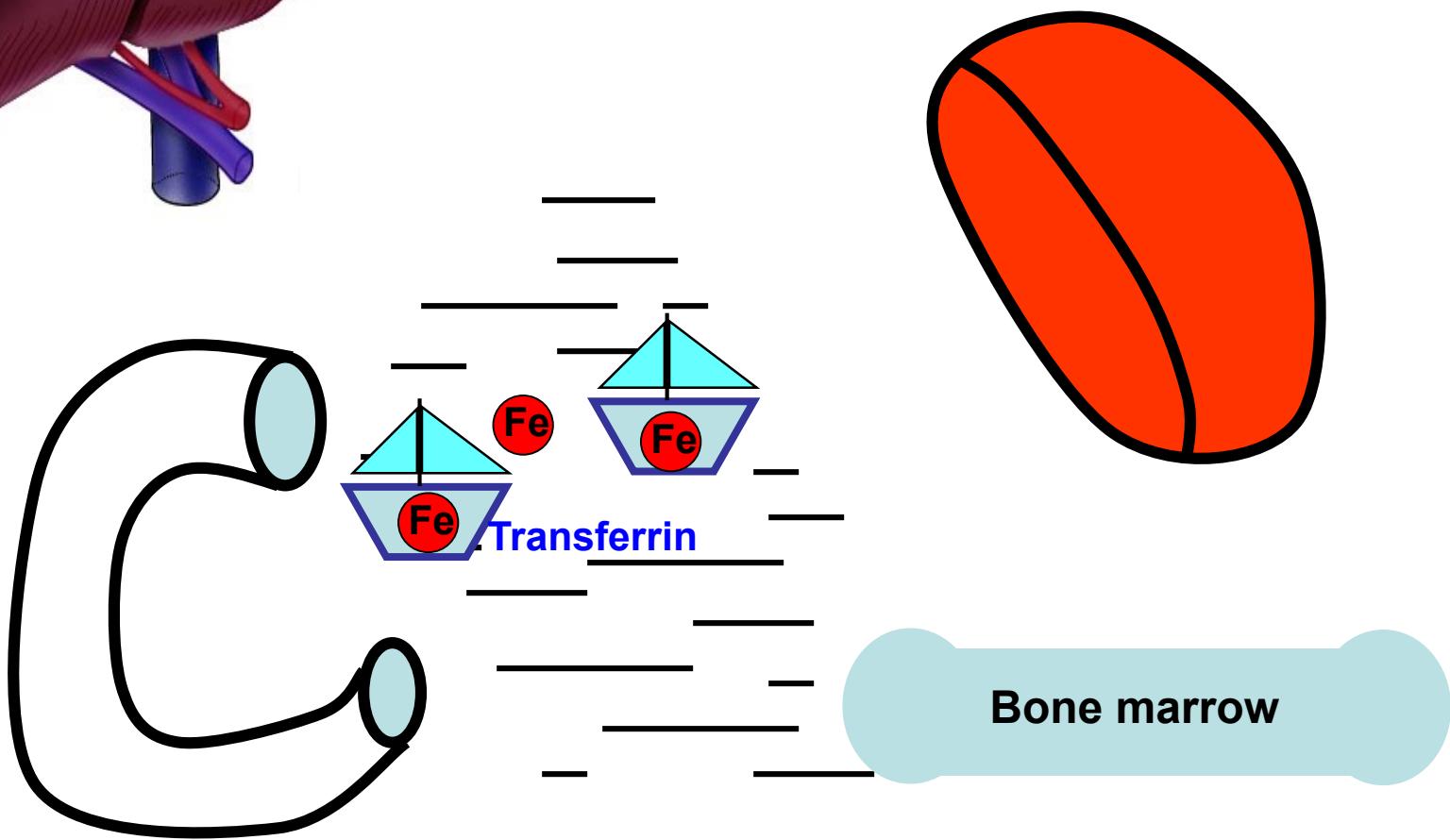
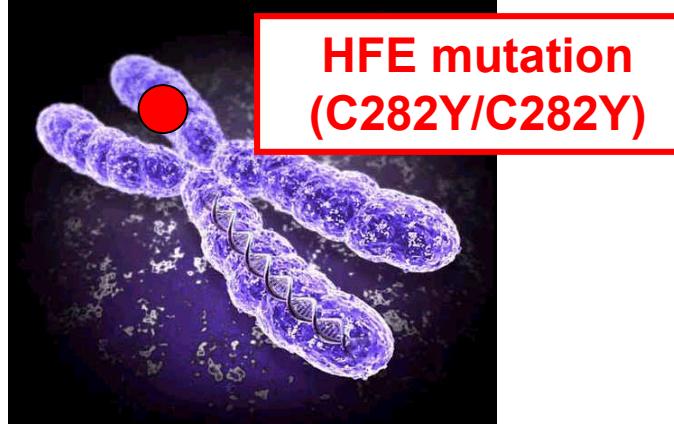
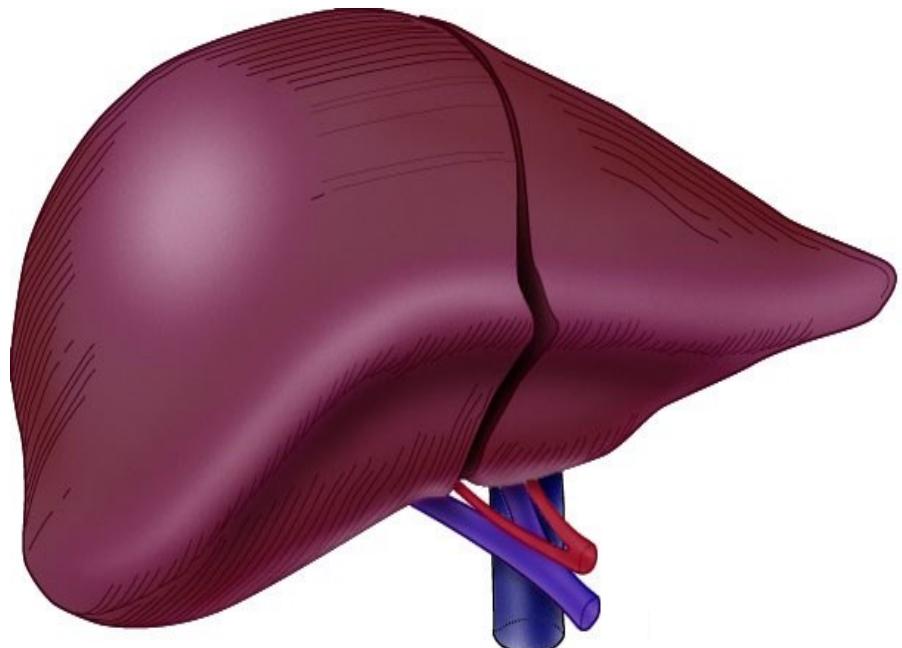
# **Evolving concepts and practices**

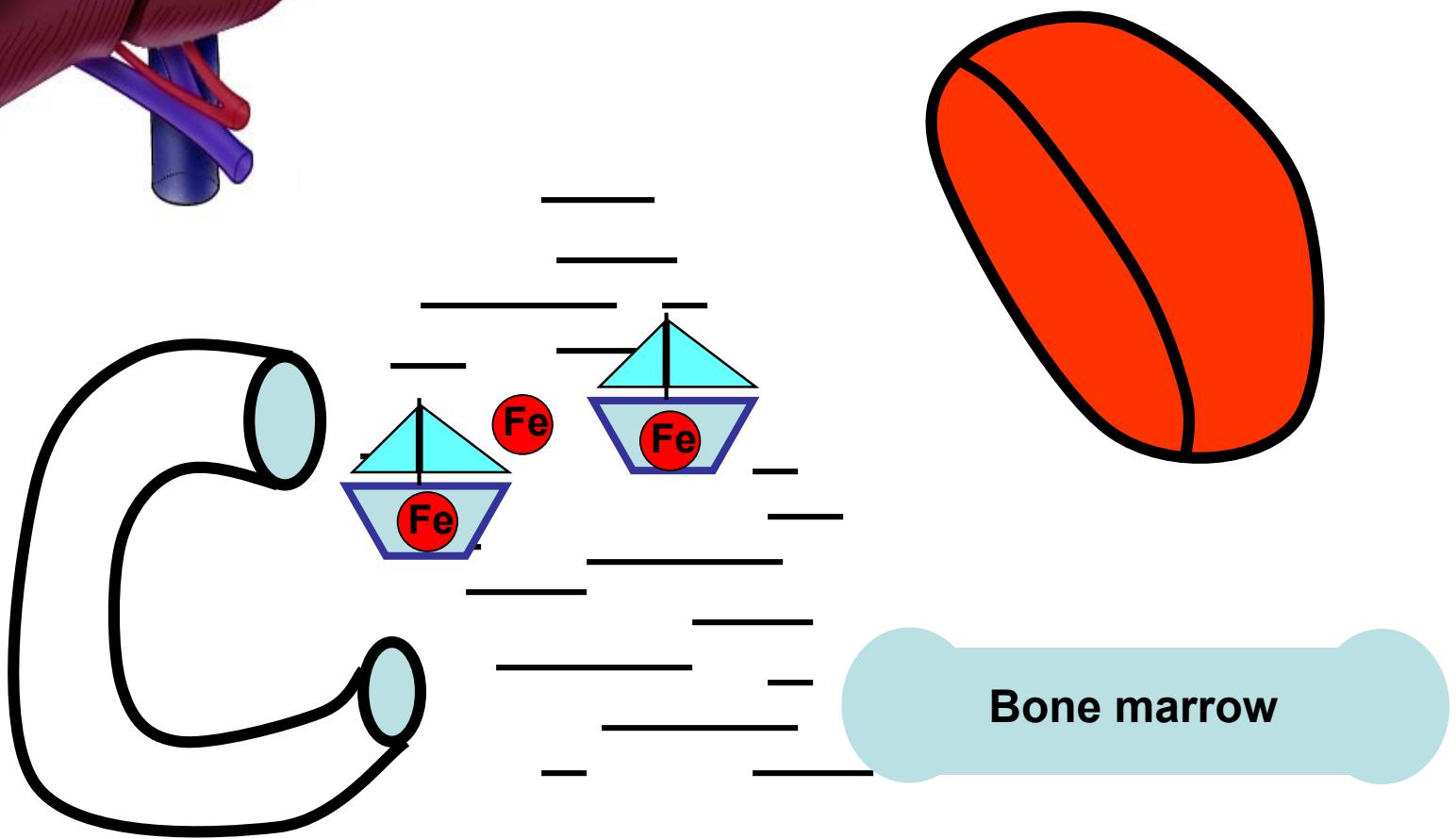
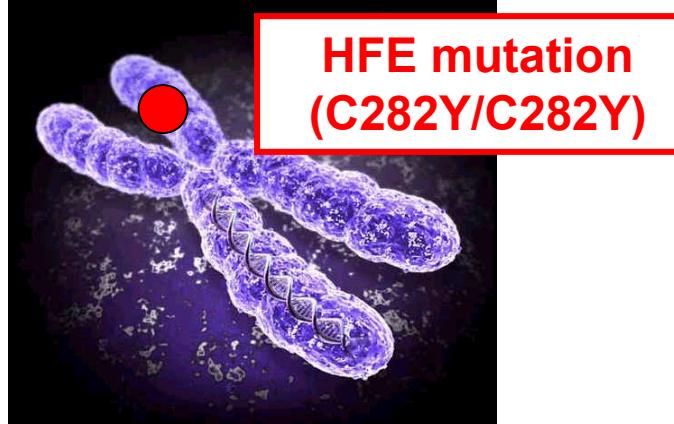
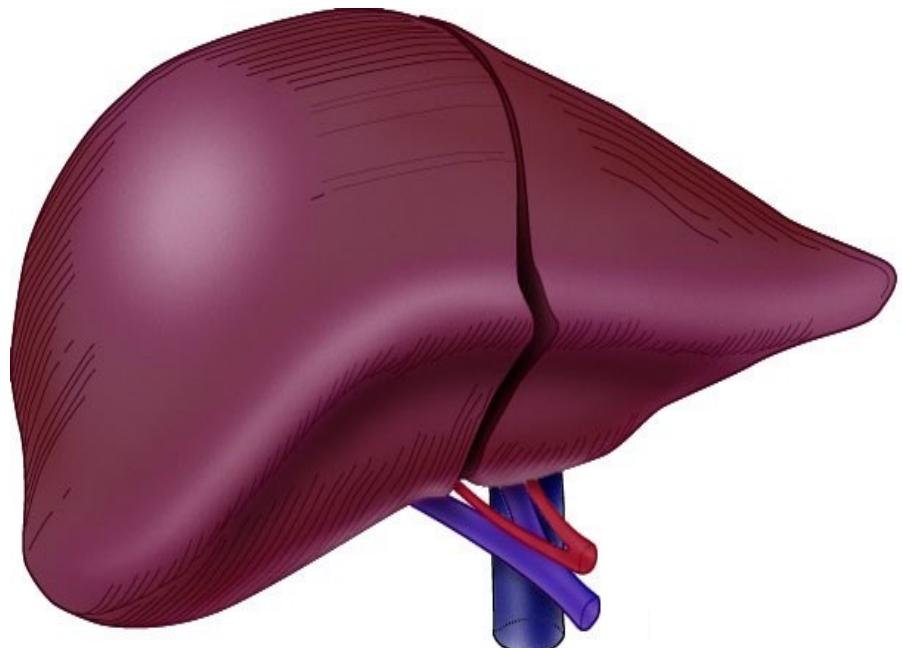
**Patho-physiology**

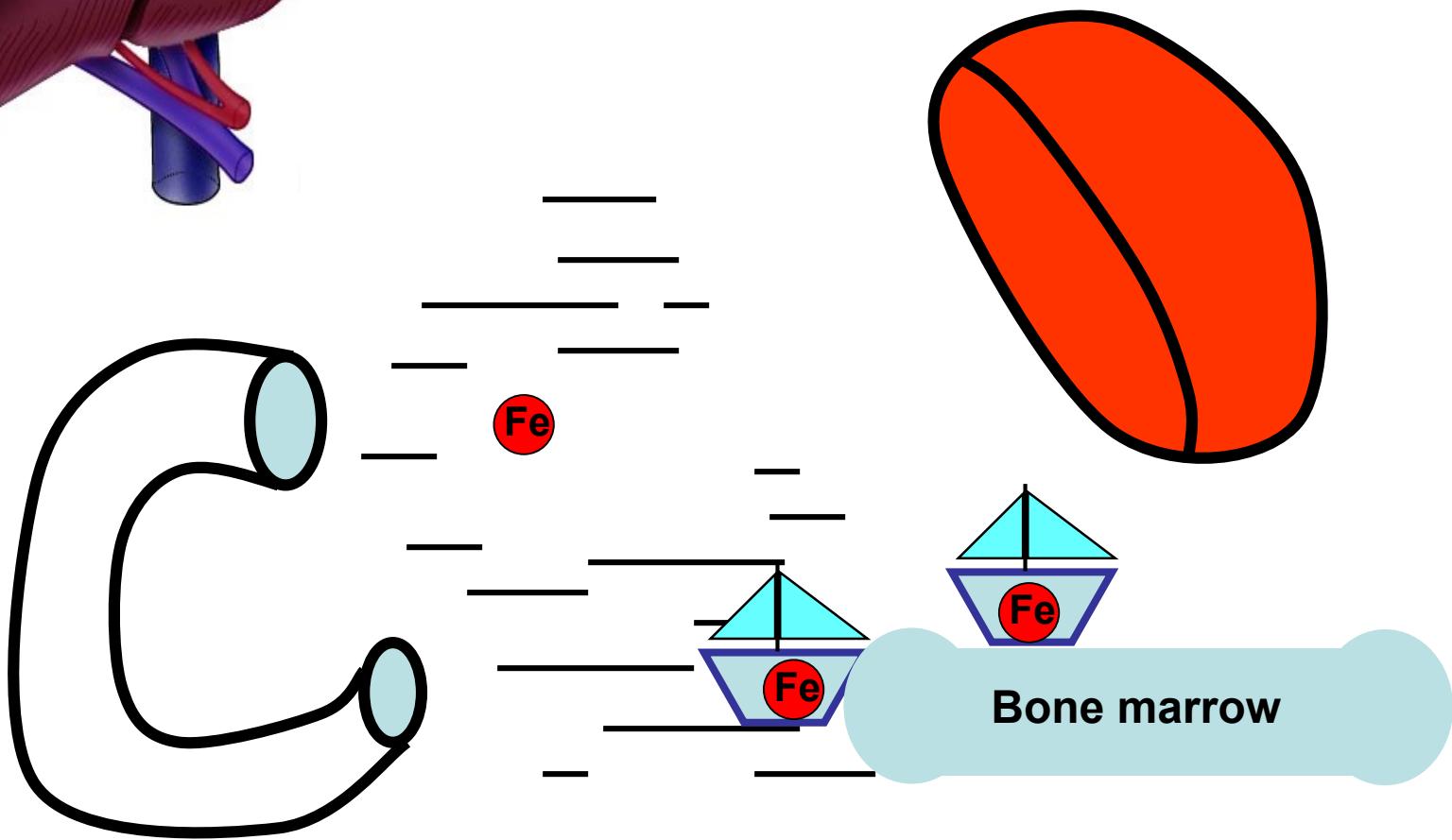
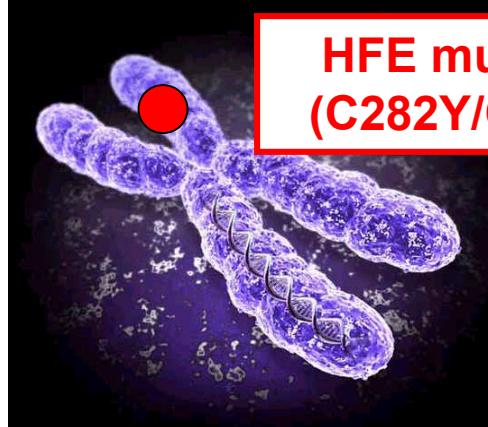
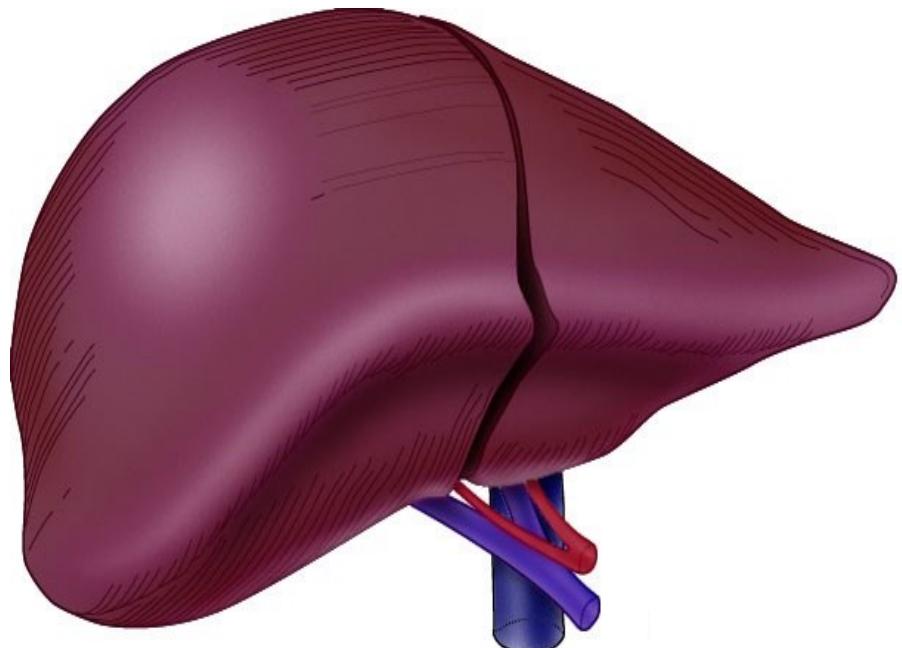
**Diagnosis**

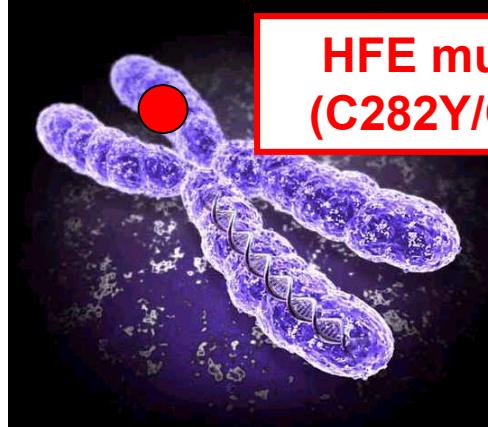
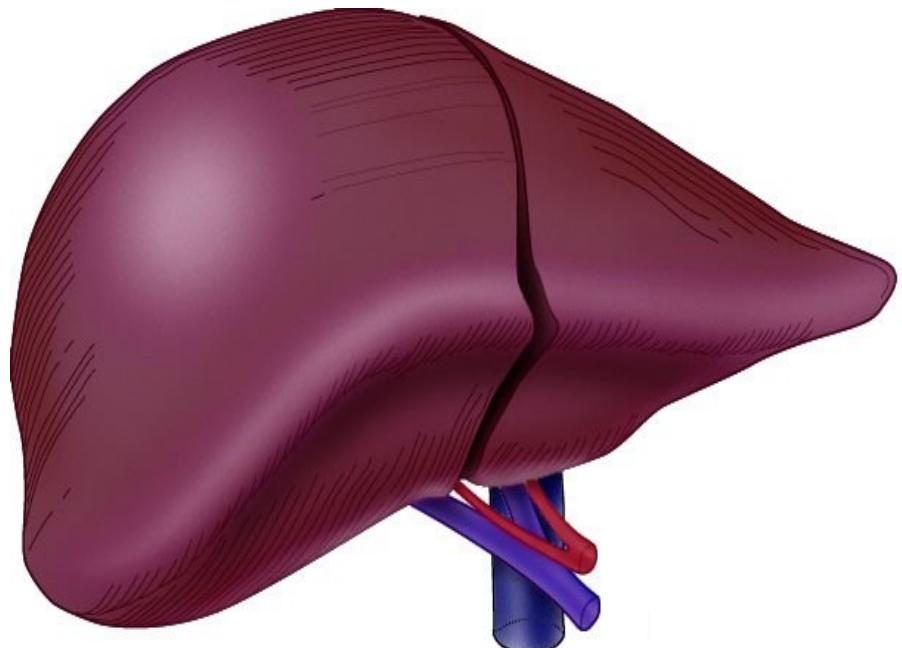
**Treatment**



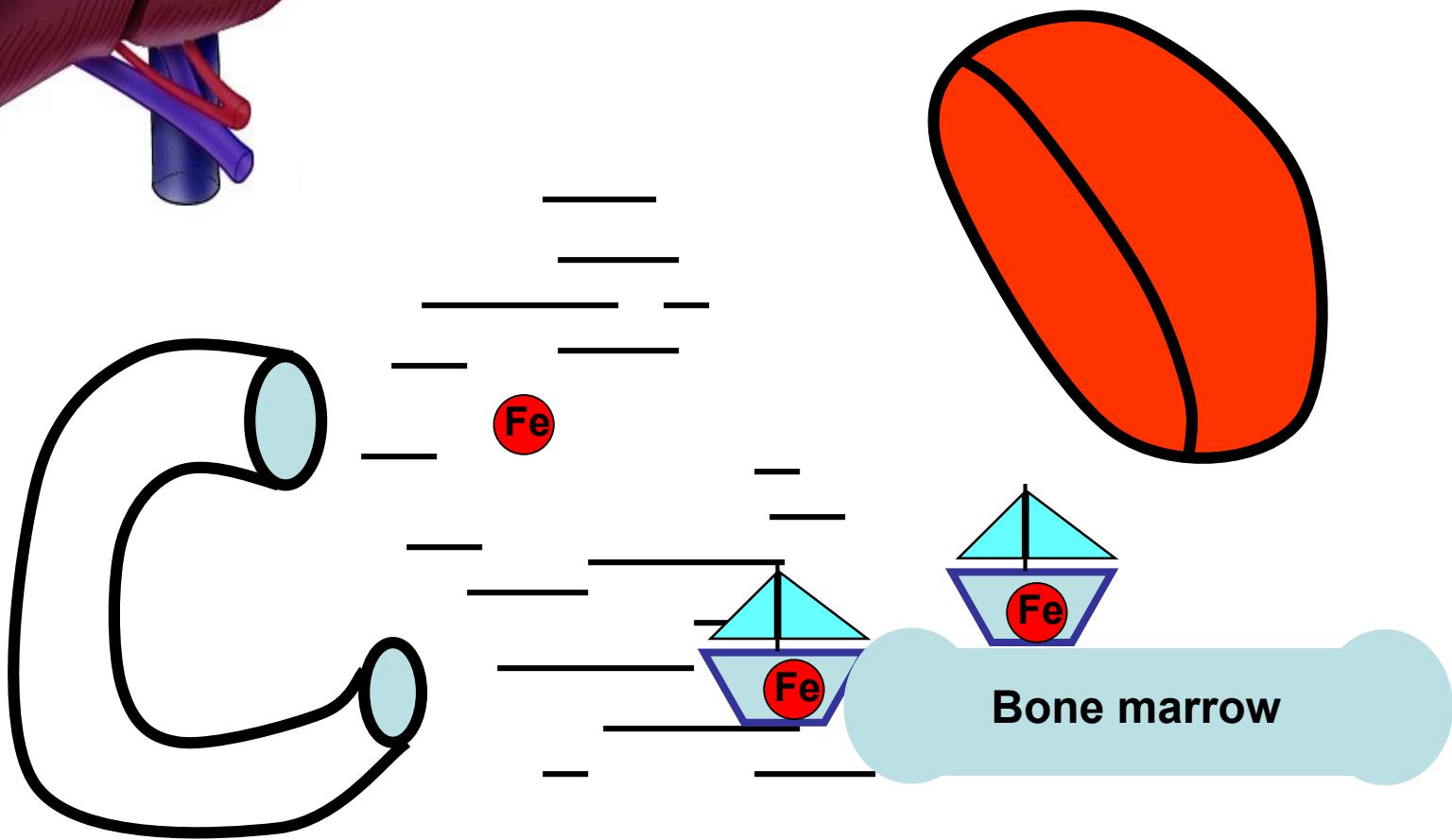


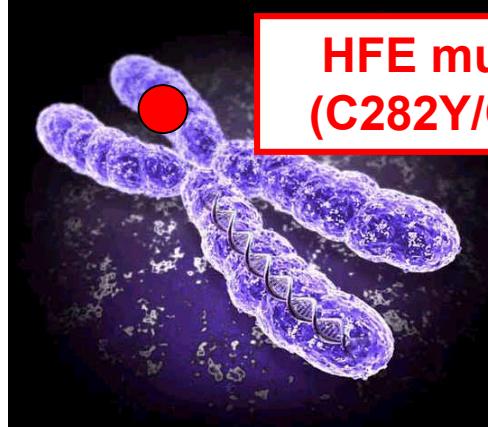
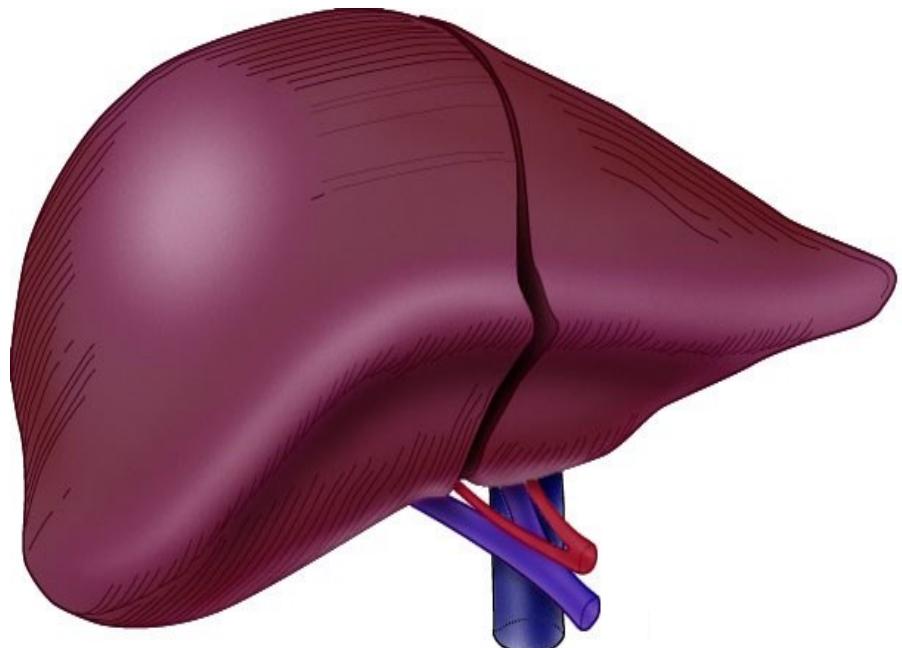




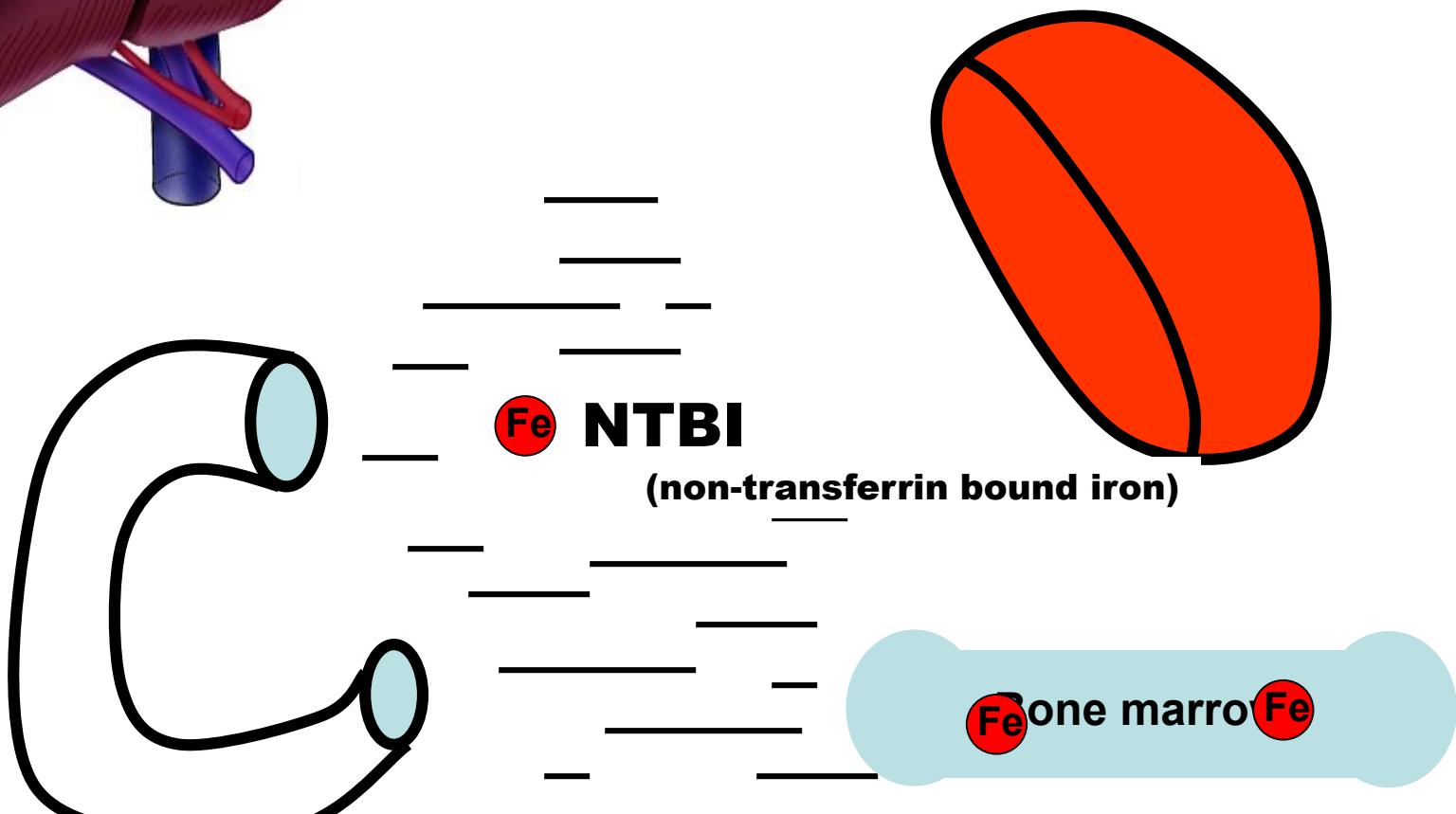


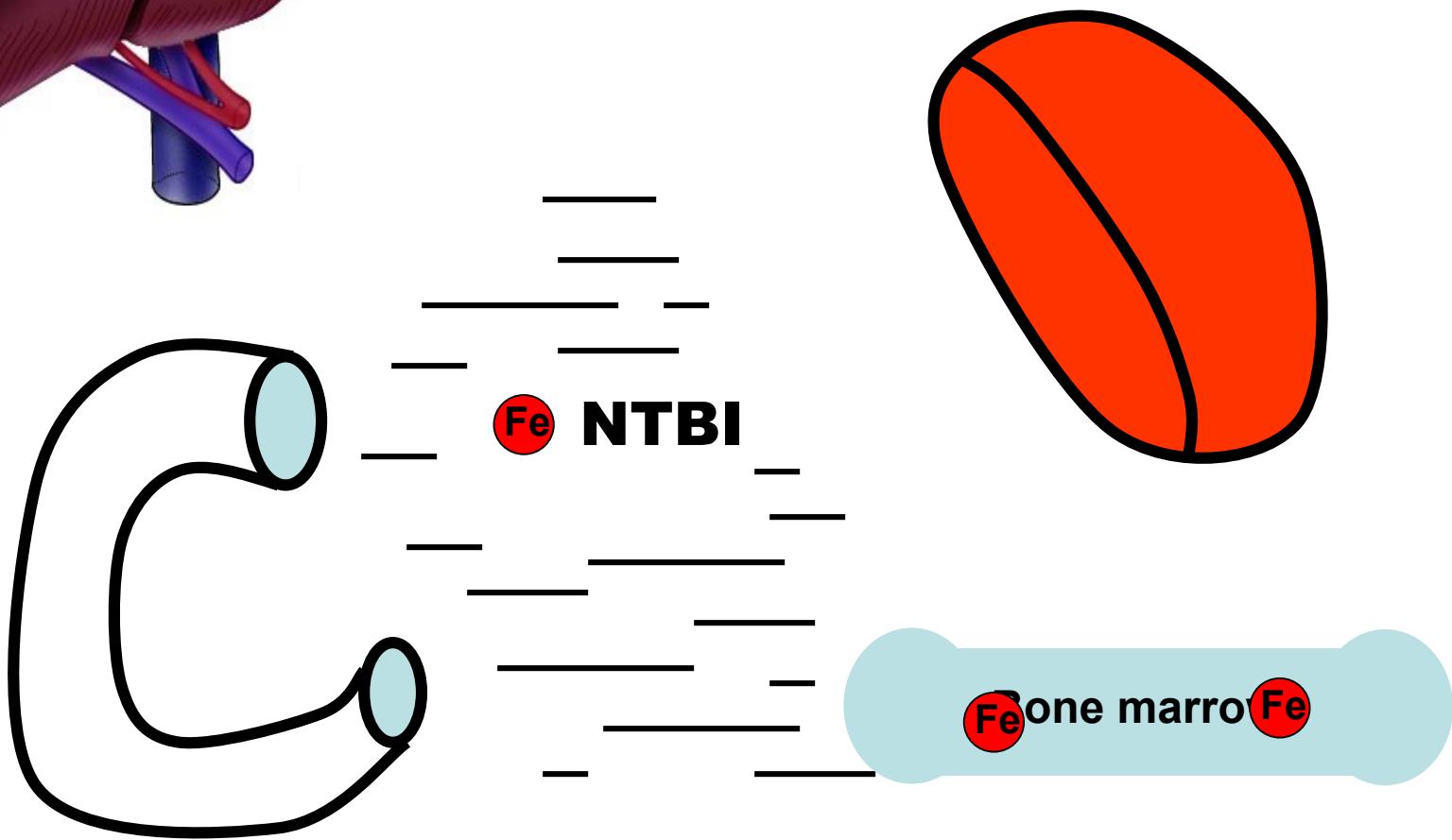
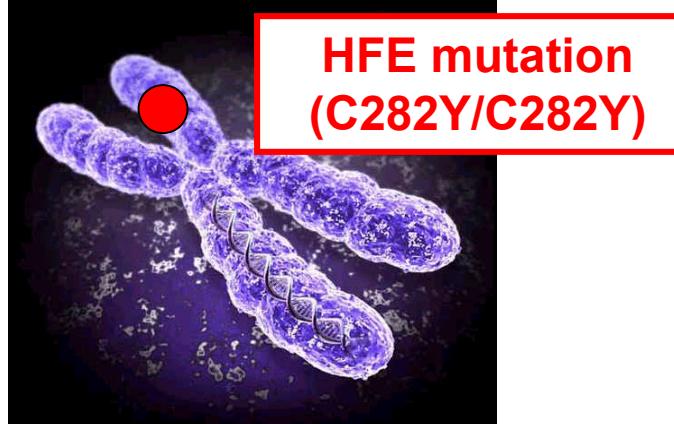
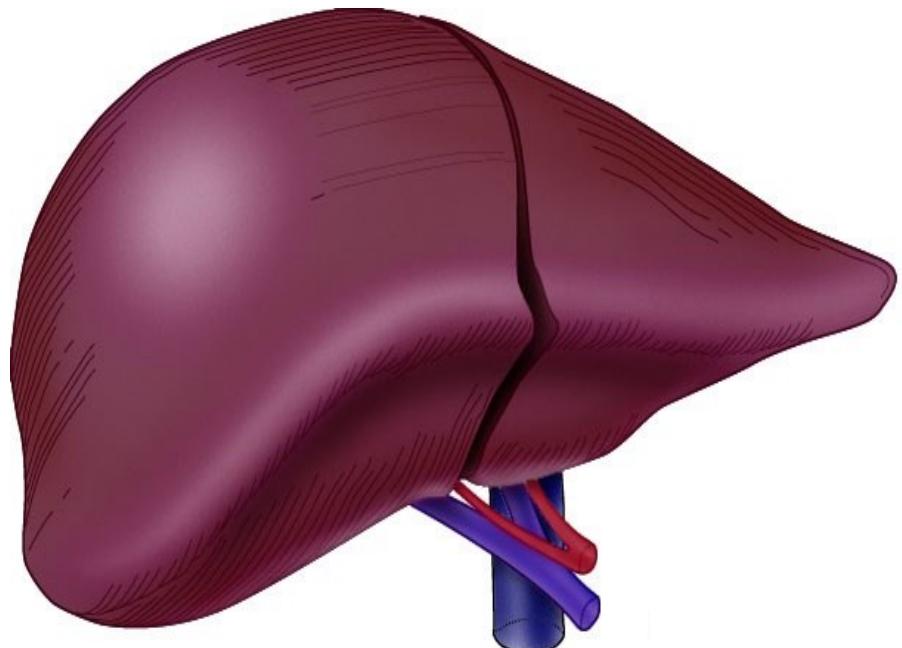
HFE mutation  
(C282Y/C282Y)

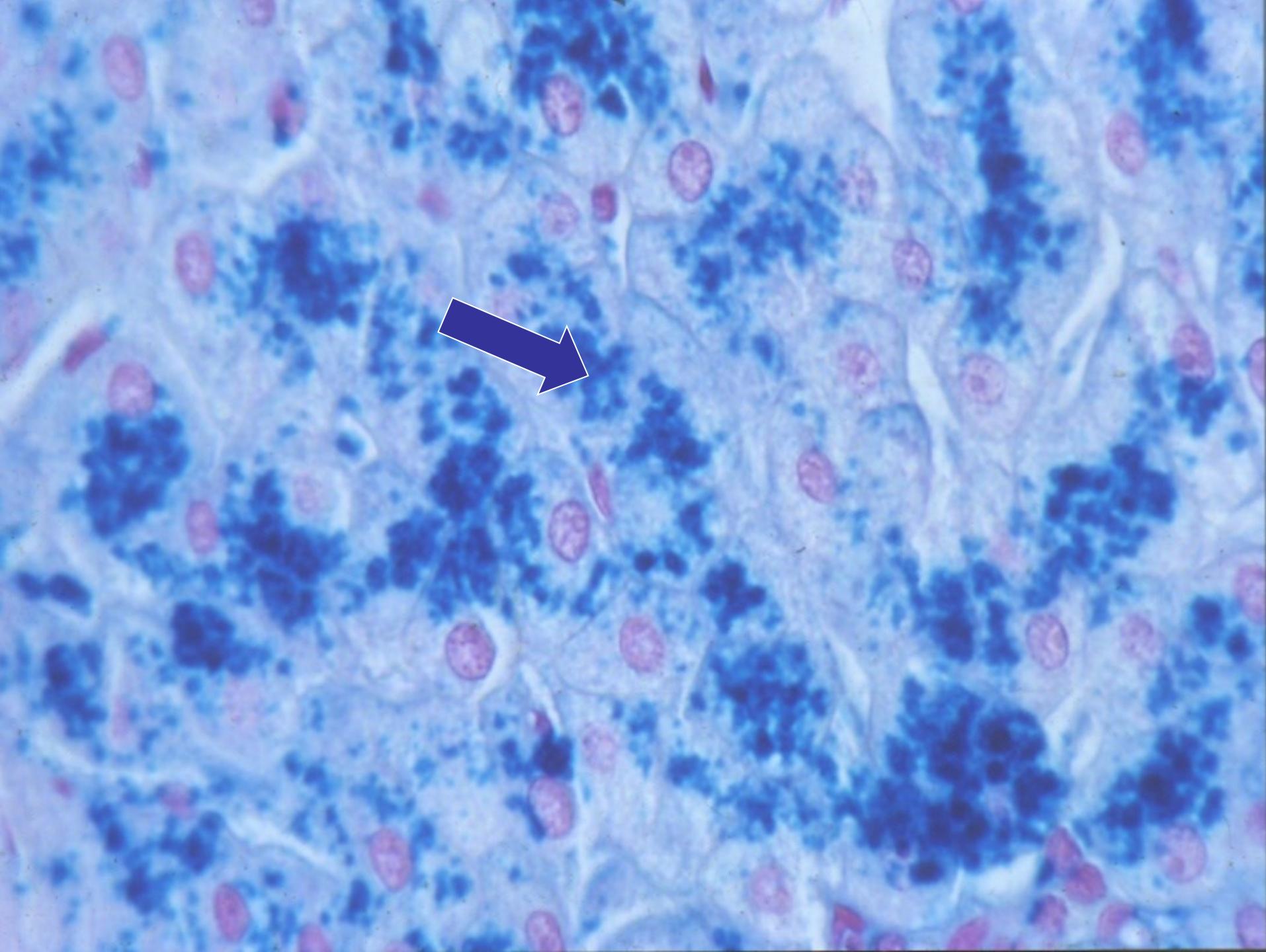


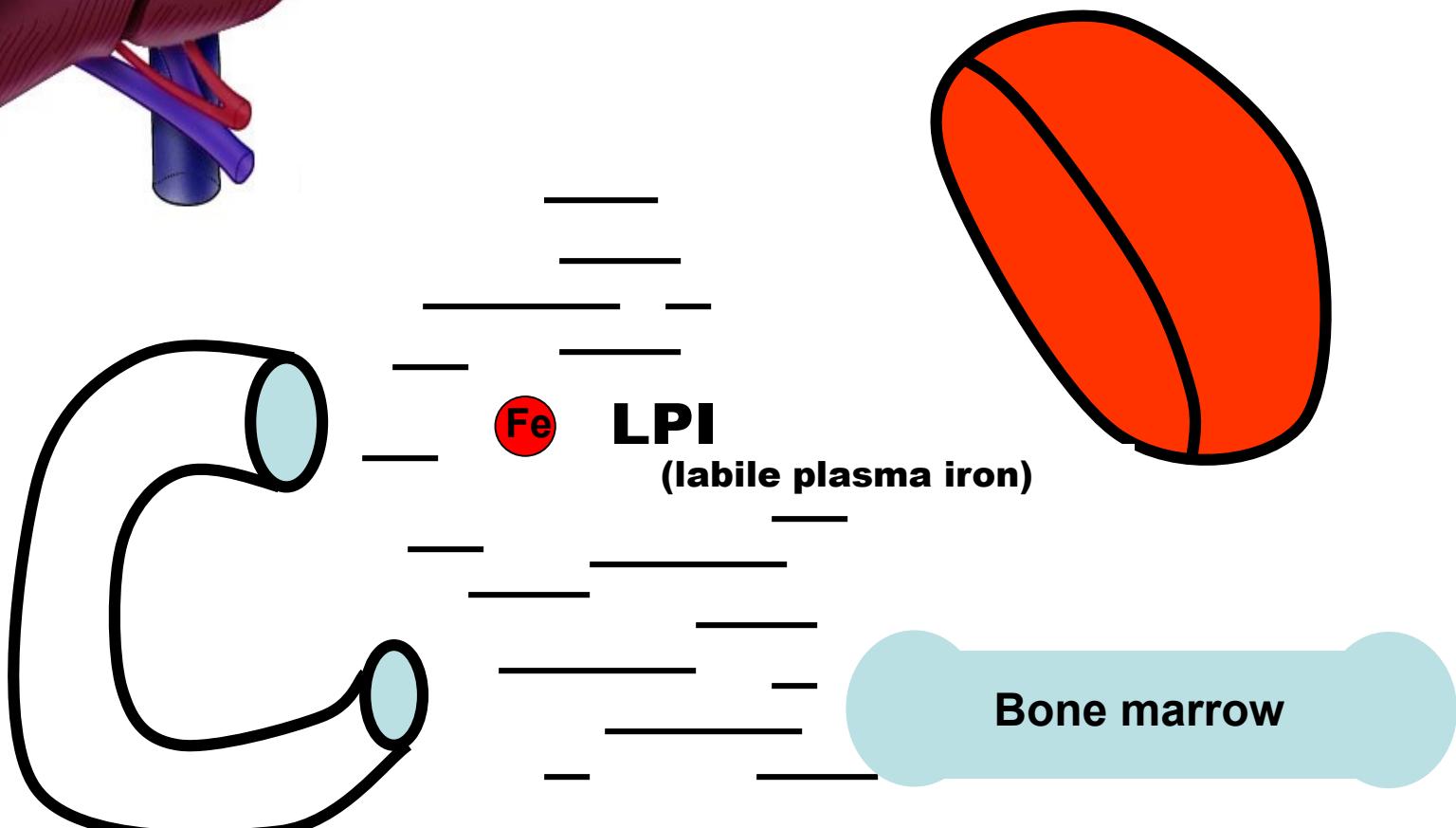
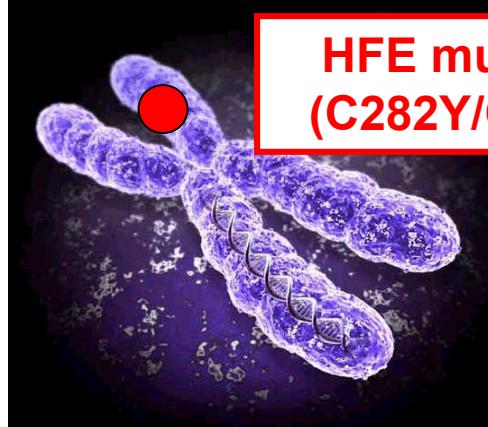
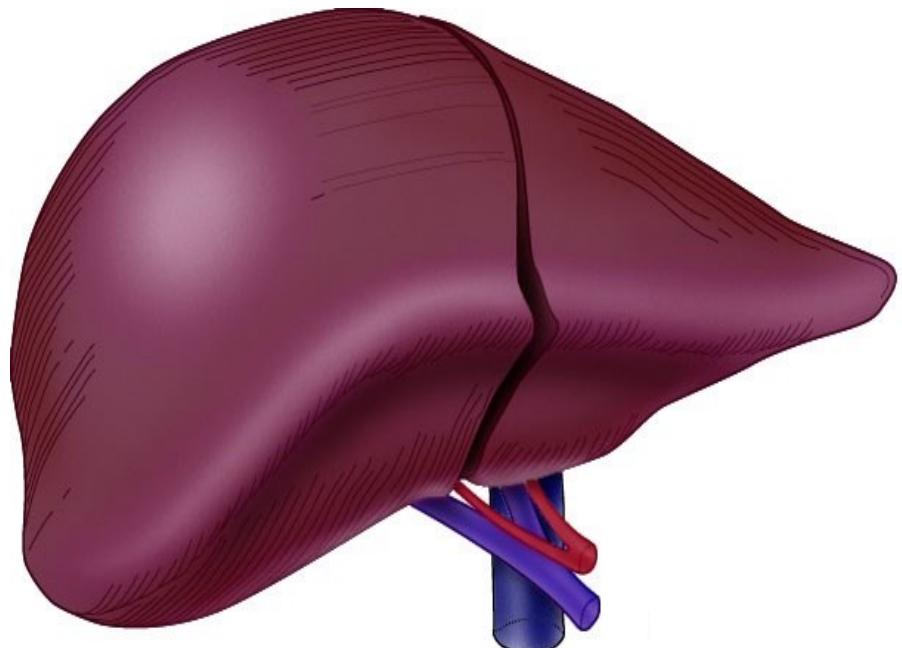


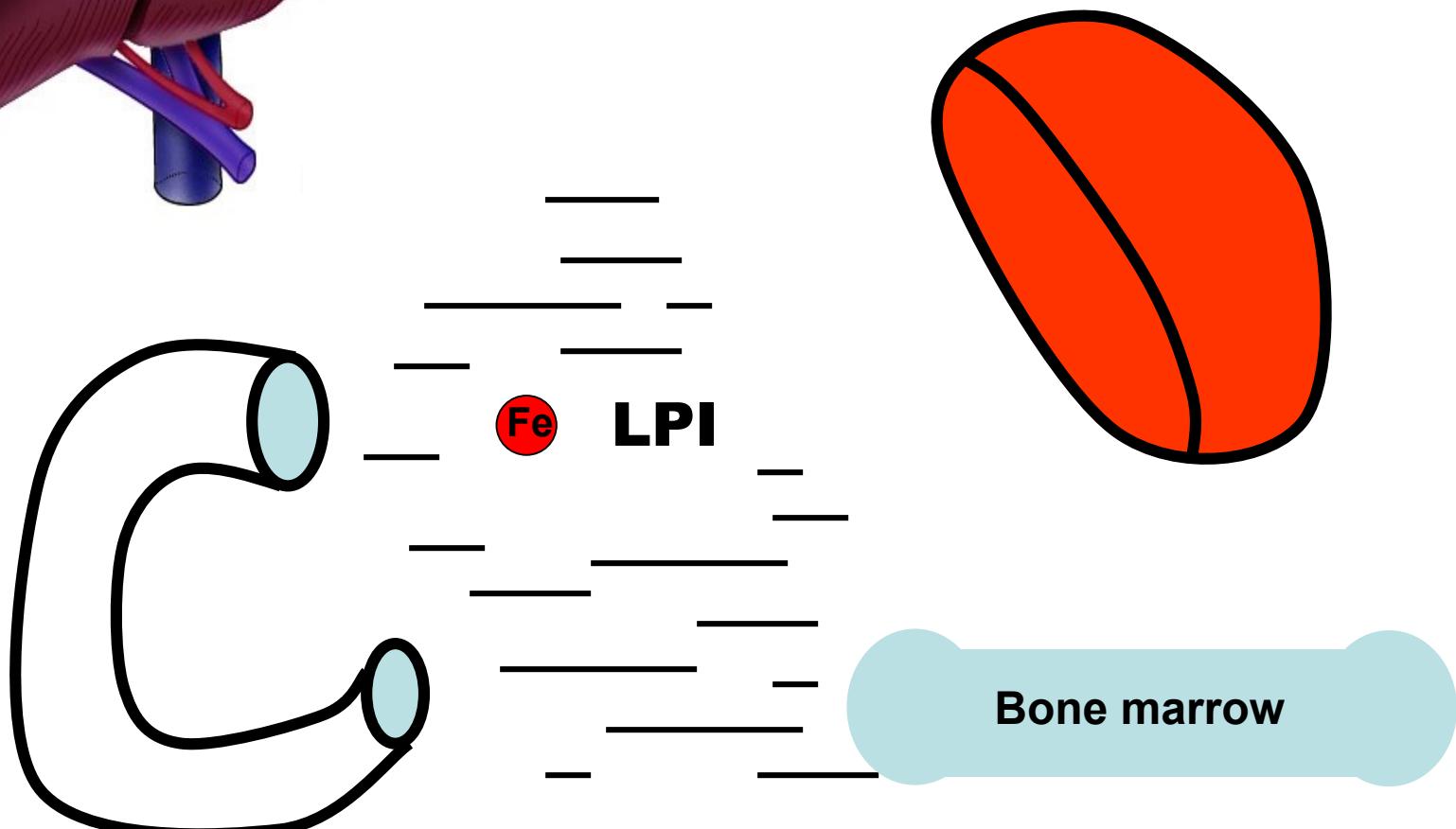
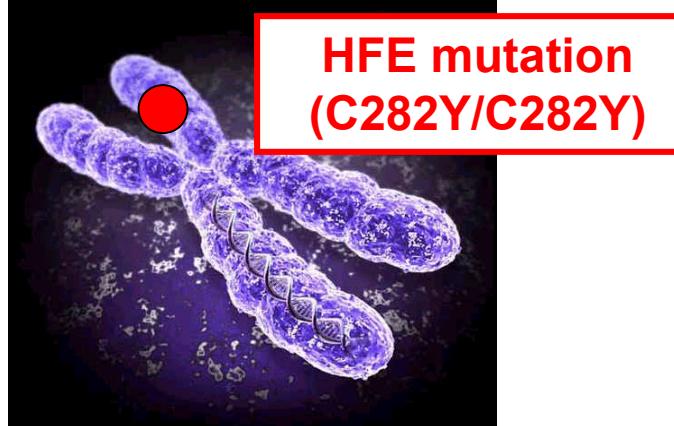
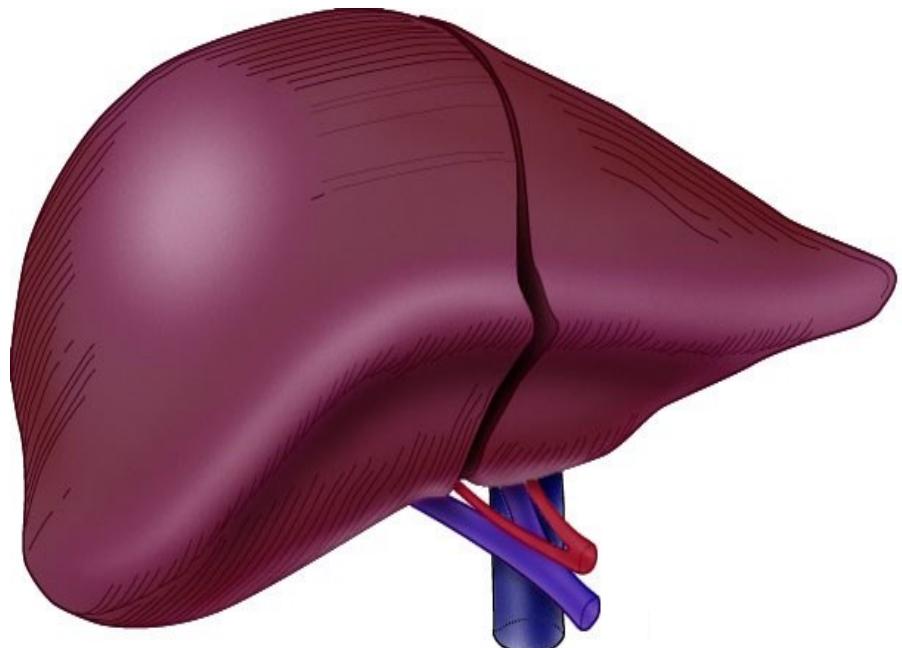
HFE mutation  
(C282Y/C282Y)

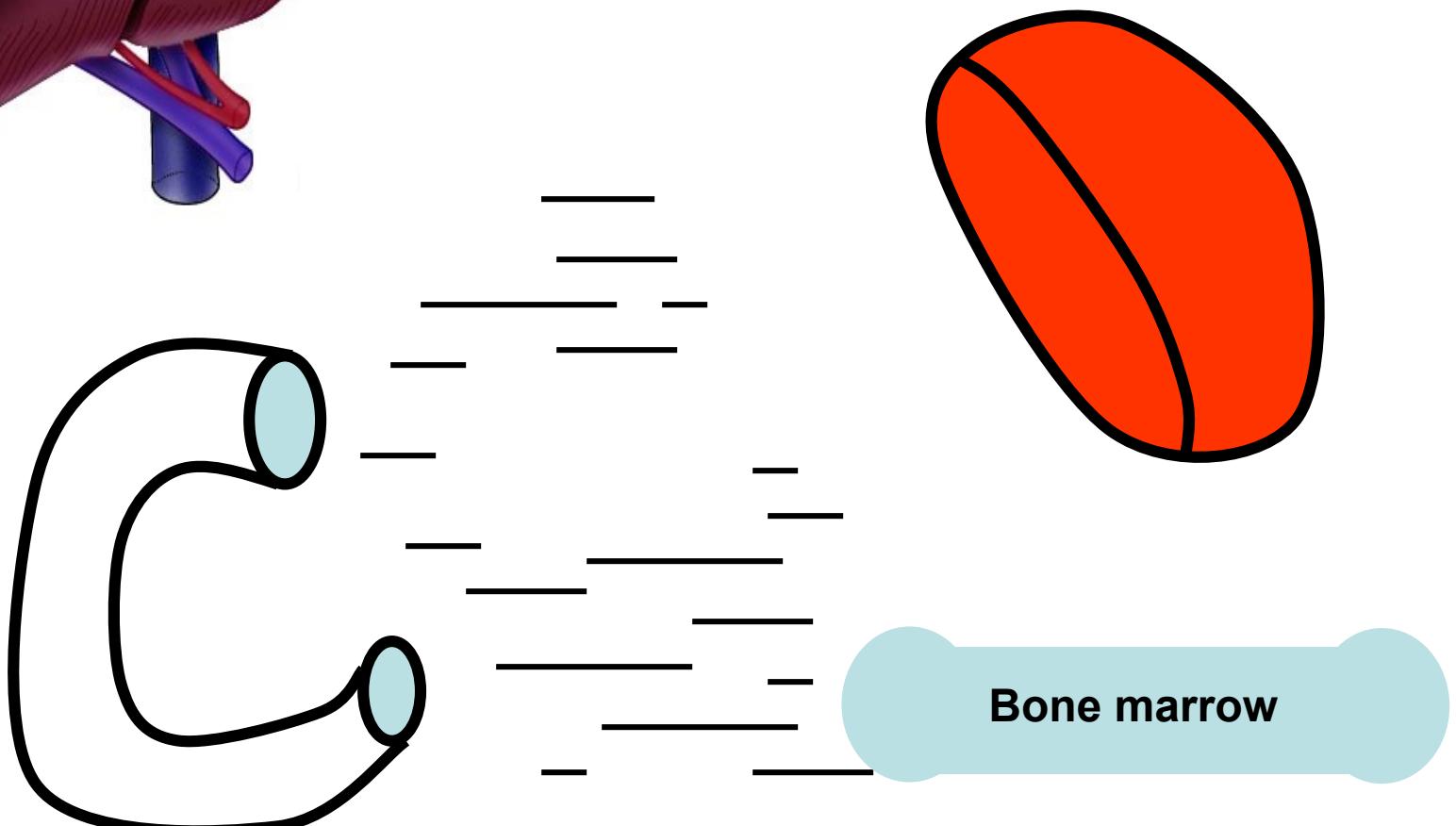
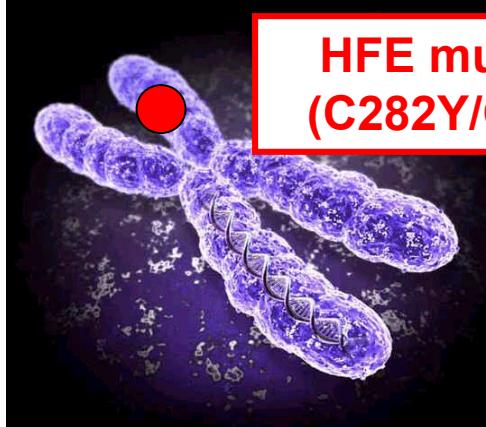
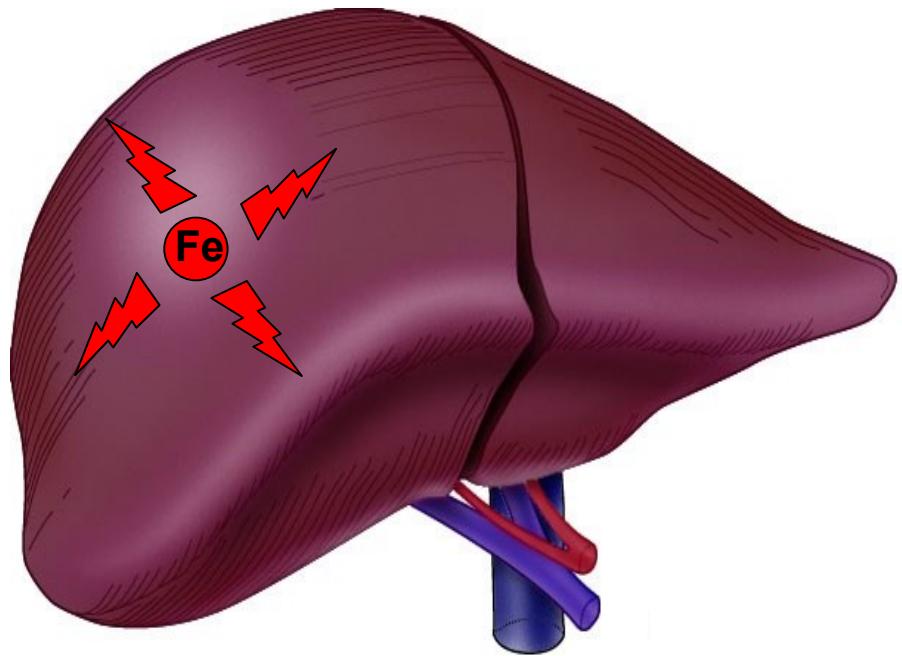




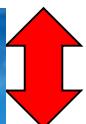






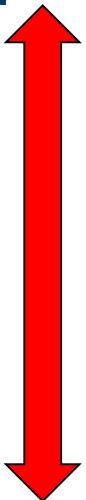






**30% M**

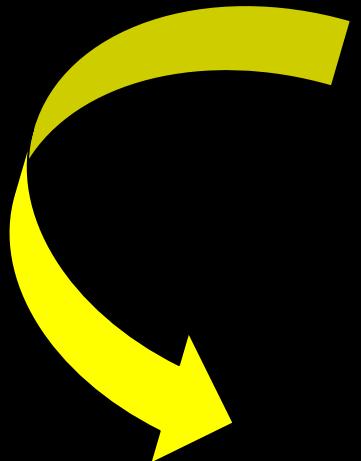
**1% F**



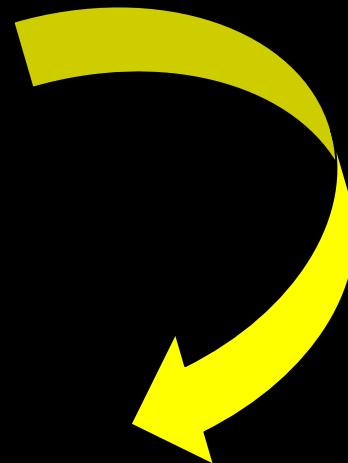
**70% M**

**99% F**

# **Phenotypic variability**



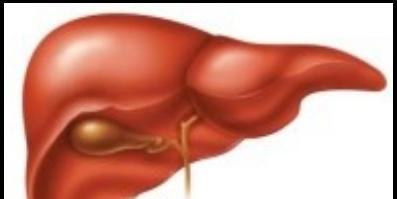
**Iron overload**



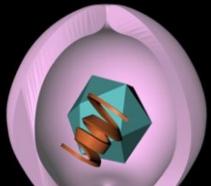
**Visceral target**



(Dostalikova-Cimburova M  
J Cell Mol Med 2014)



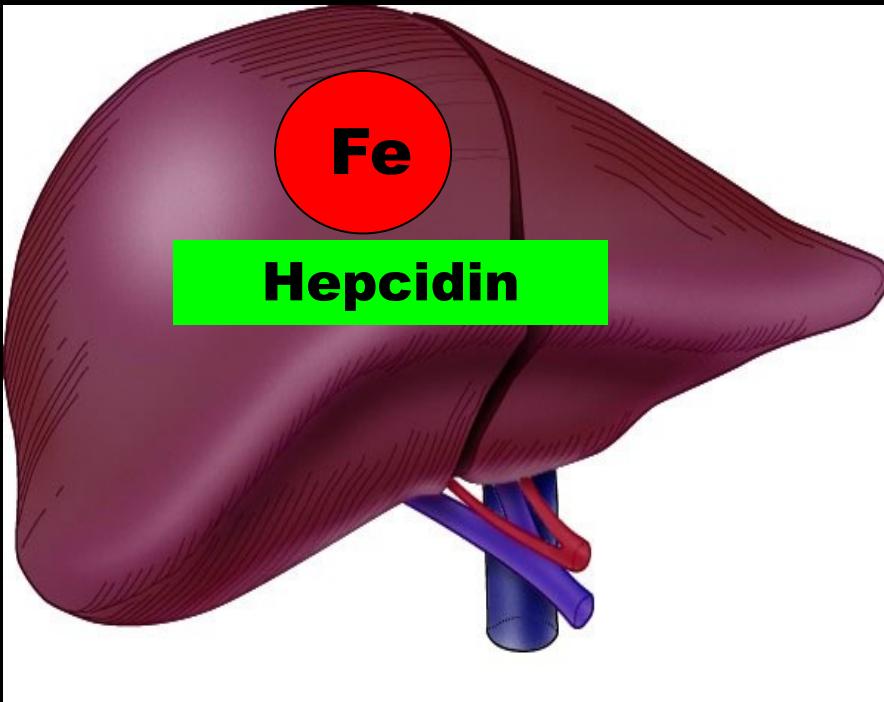
(Detivaud L Blood 2005)



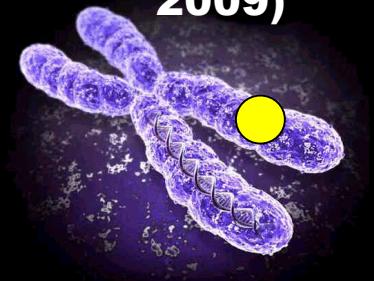
(Girelli D J Hepatol 2009)



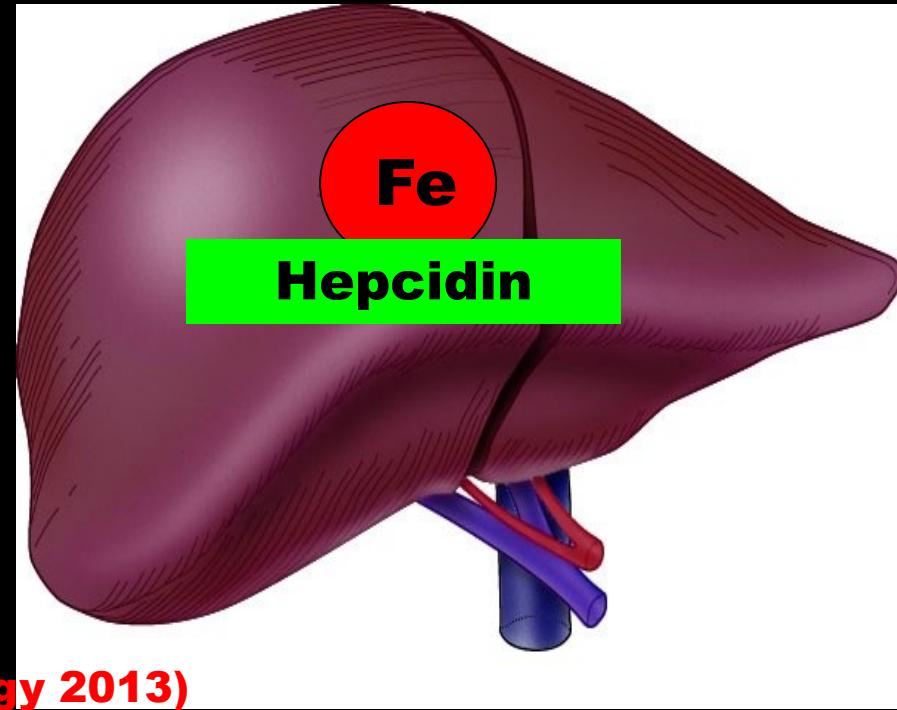
(Liu Q JCI 2012)



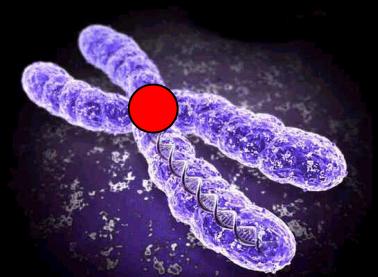
Hepcidin  
promoter  
(Island ML  
Haematologica  
2009)



Low CD8  
(Costa M  
Plos One  
2013)

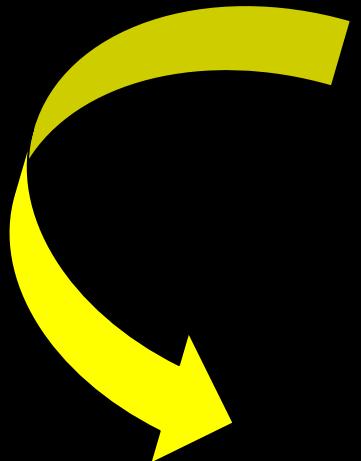


(Desgranges R Hepatology 2013)

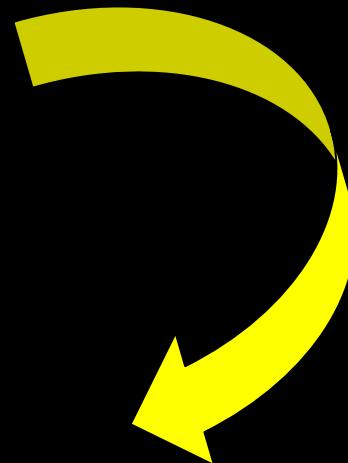


**TMPRSS6**  
**(Guo S JCI 2013)**

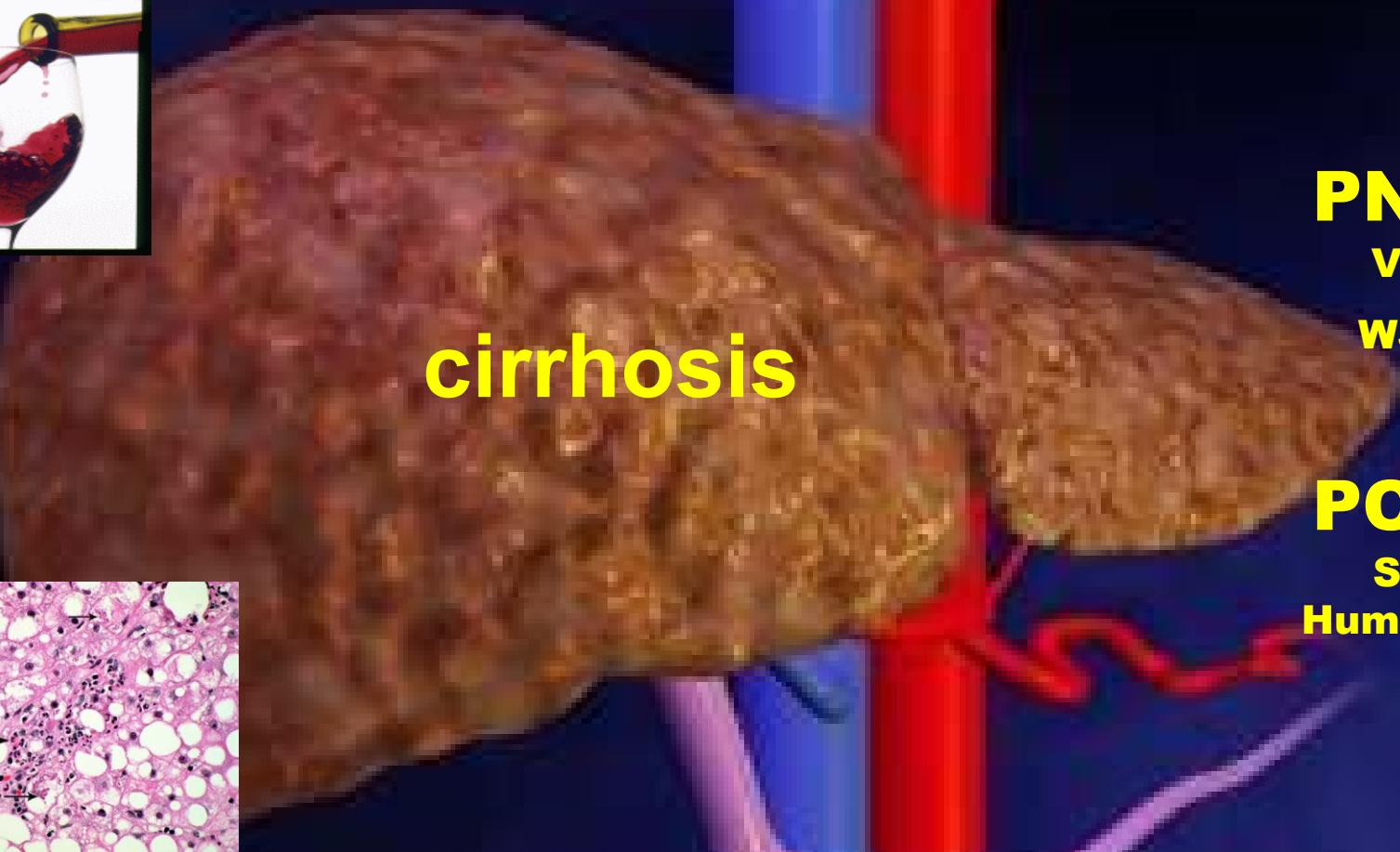
# **Phenotypic variability**



**Iron overload**



**Visceral target**



**PNPLA3**

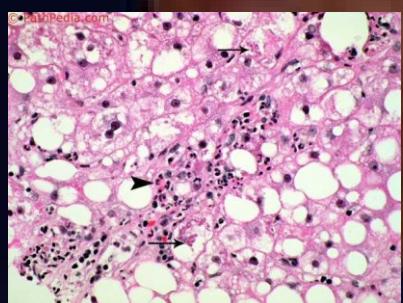
Valenti L

WJG 2013

**PCSK7**

Stickel F

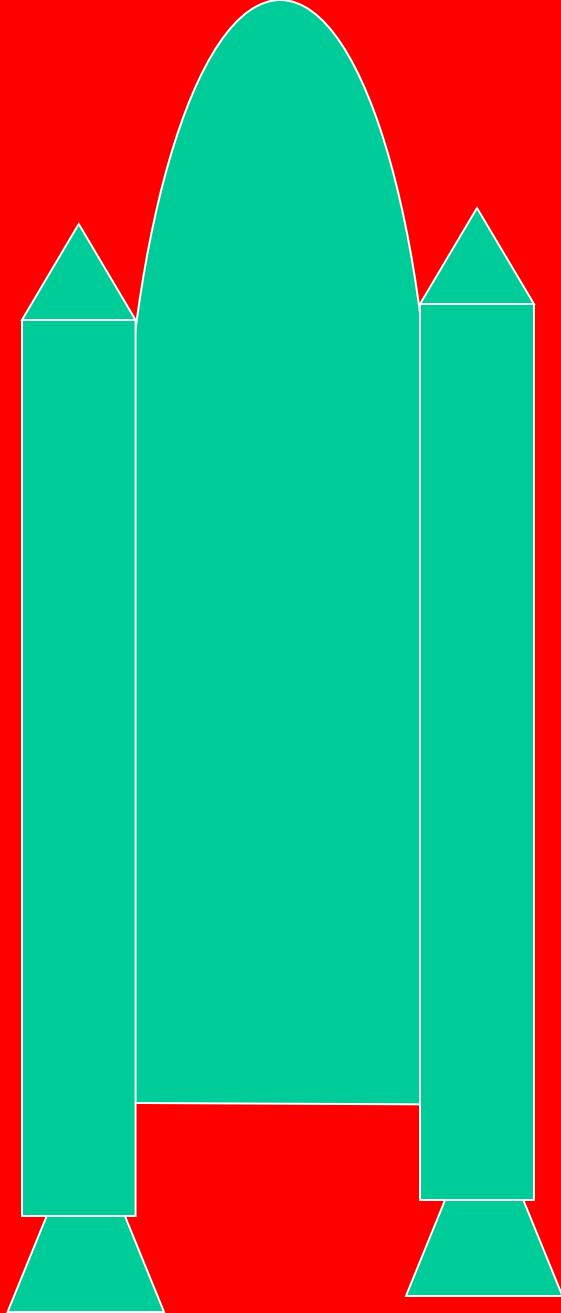
Hum Mol Genet  
2014

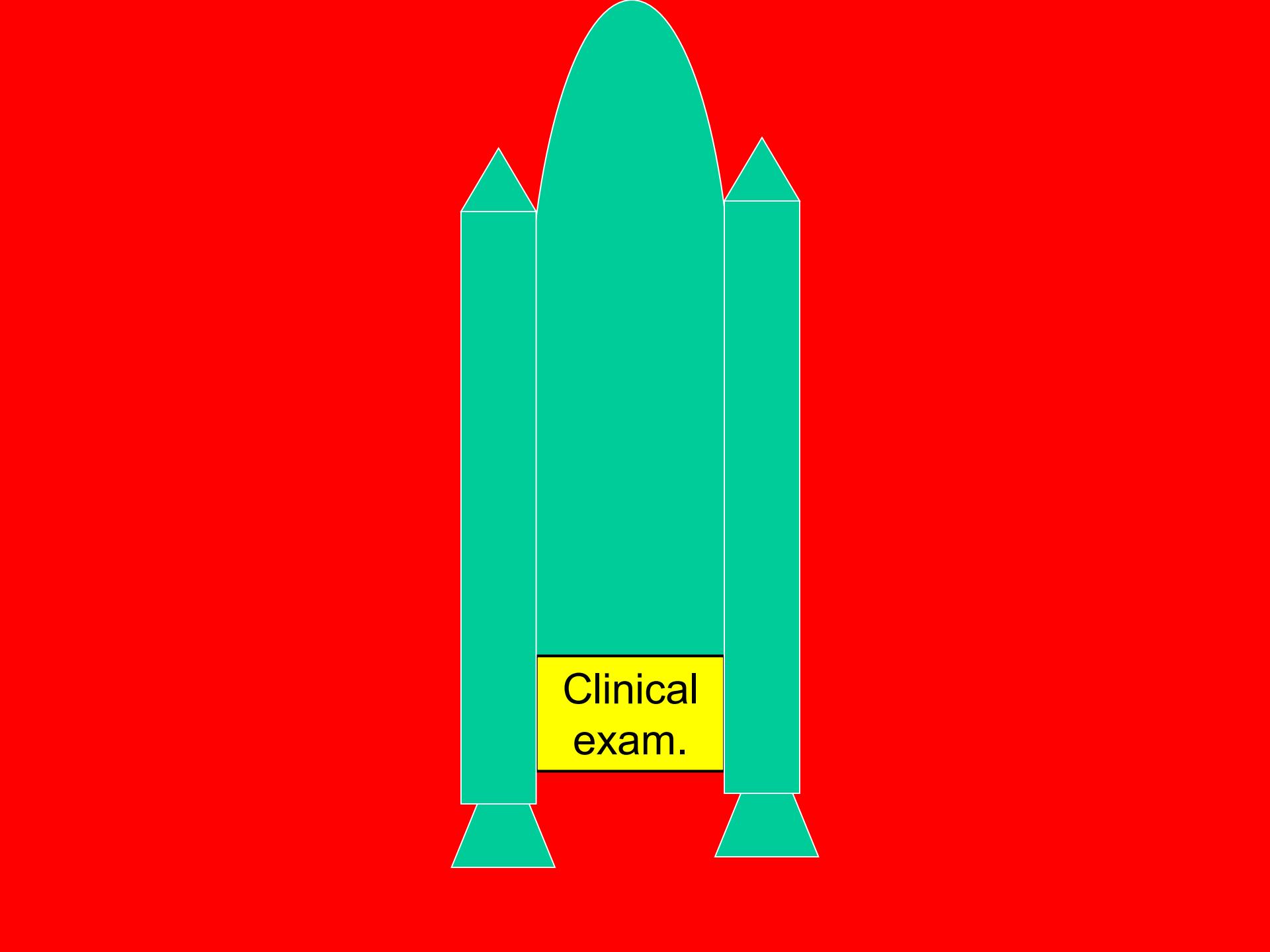


**Patho-physiology**

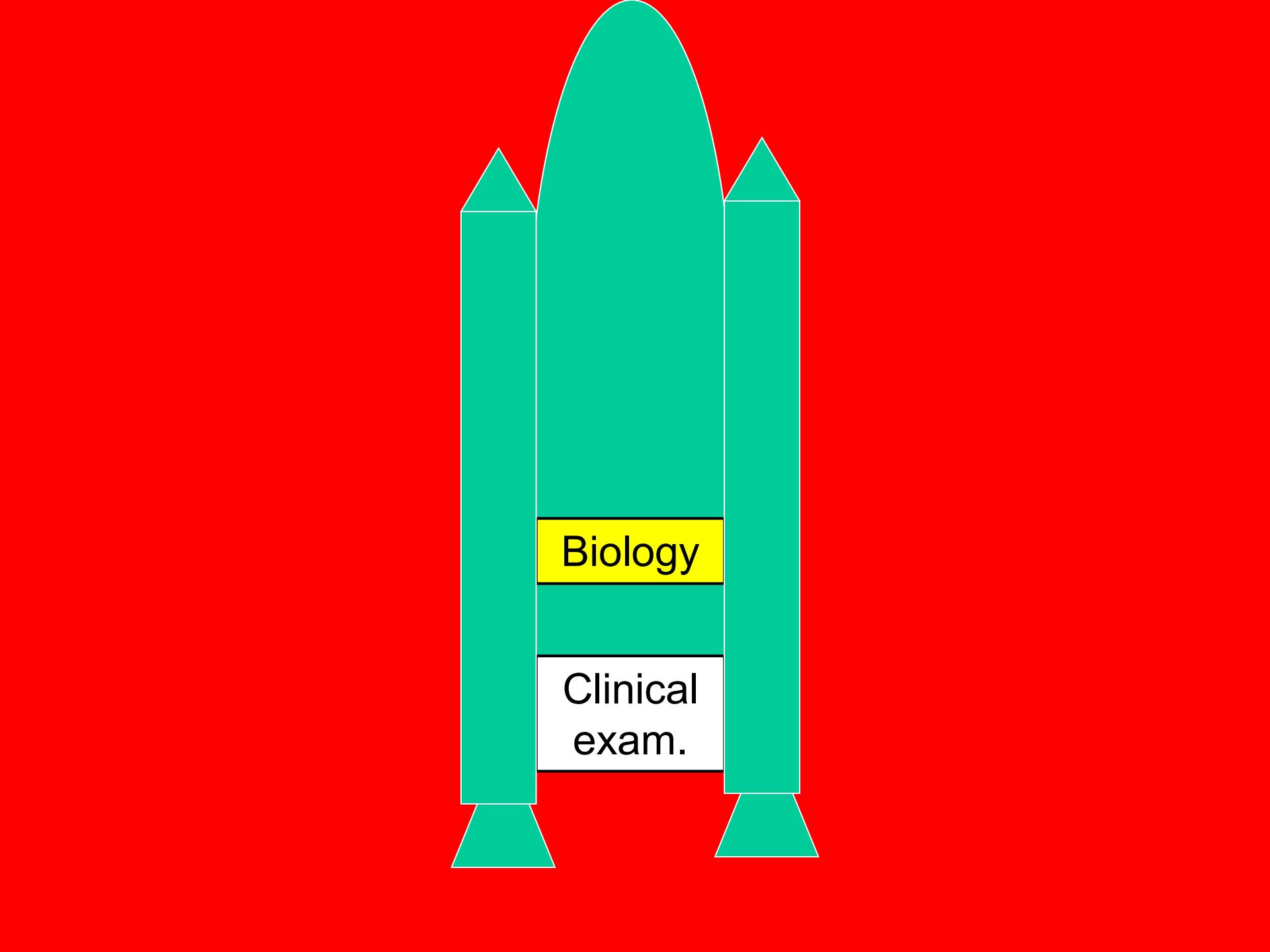
**Diagnosis**

**Treatment**



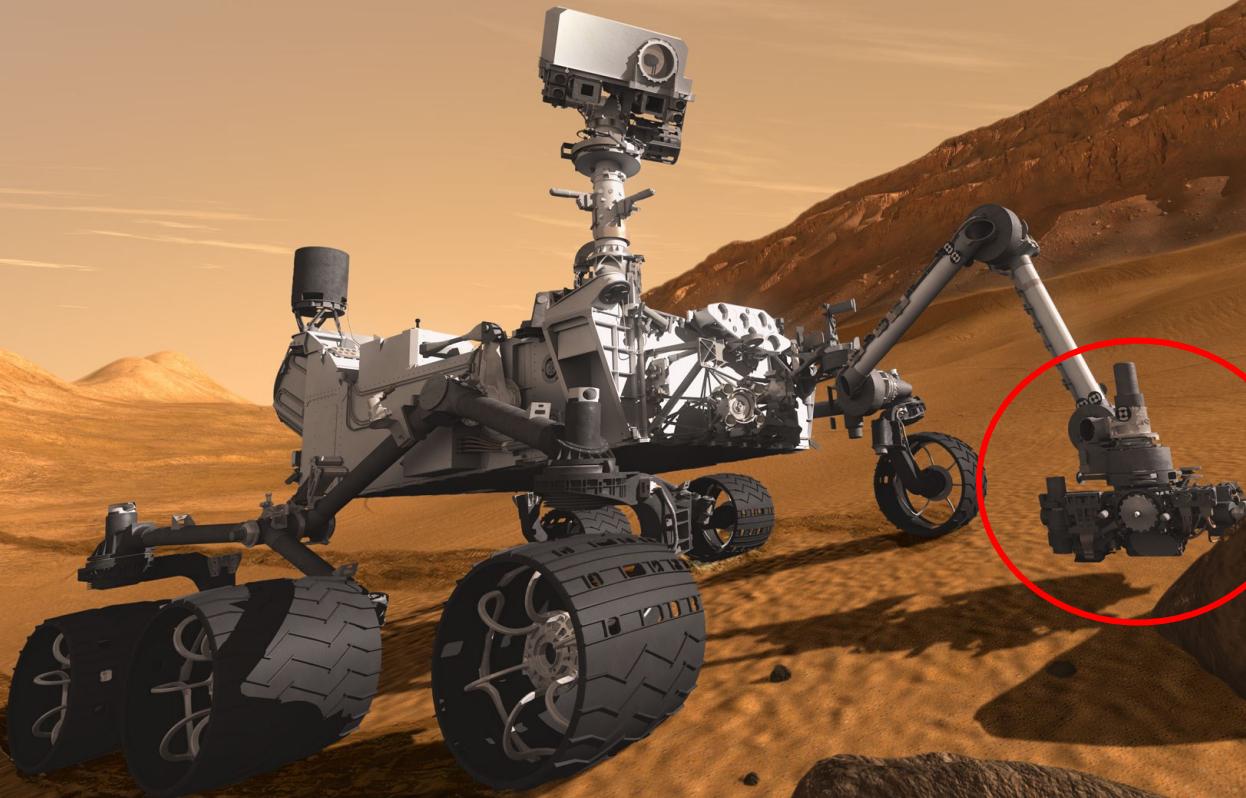


Clinical  
exam.

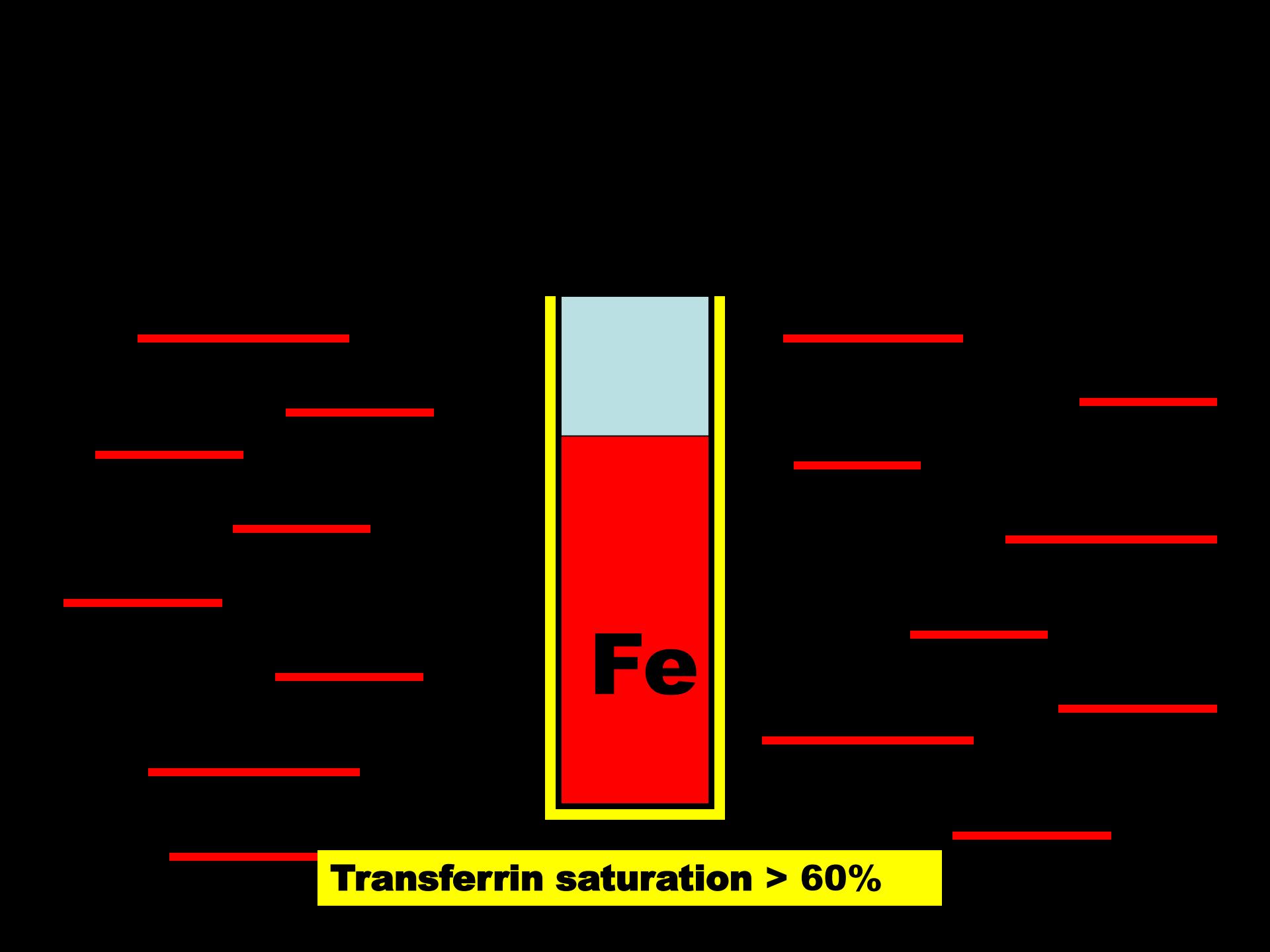


Biology

Clinical  
exam.



**Biochemical  
analyses**



**Fe**

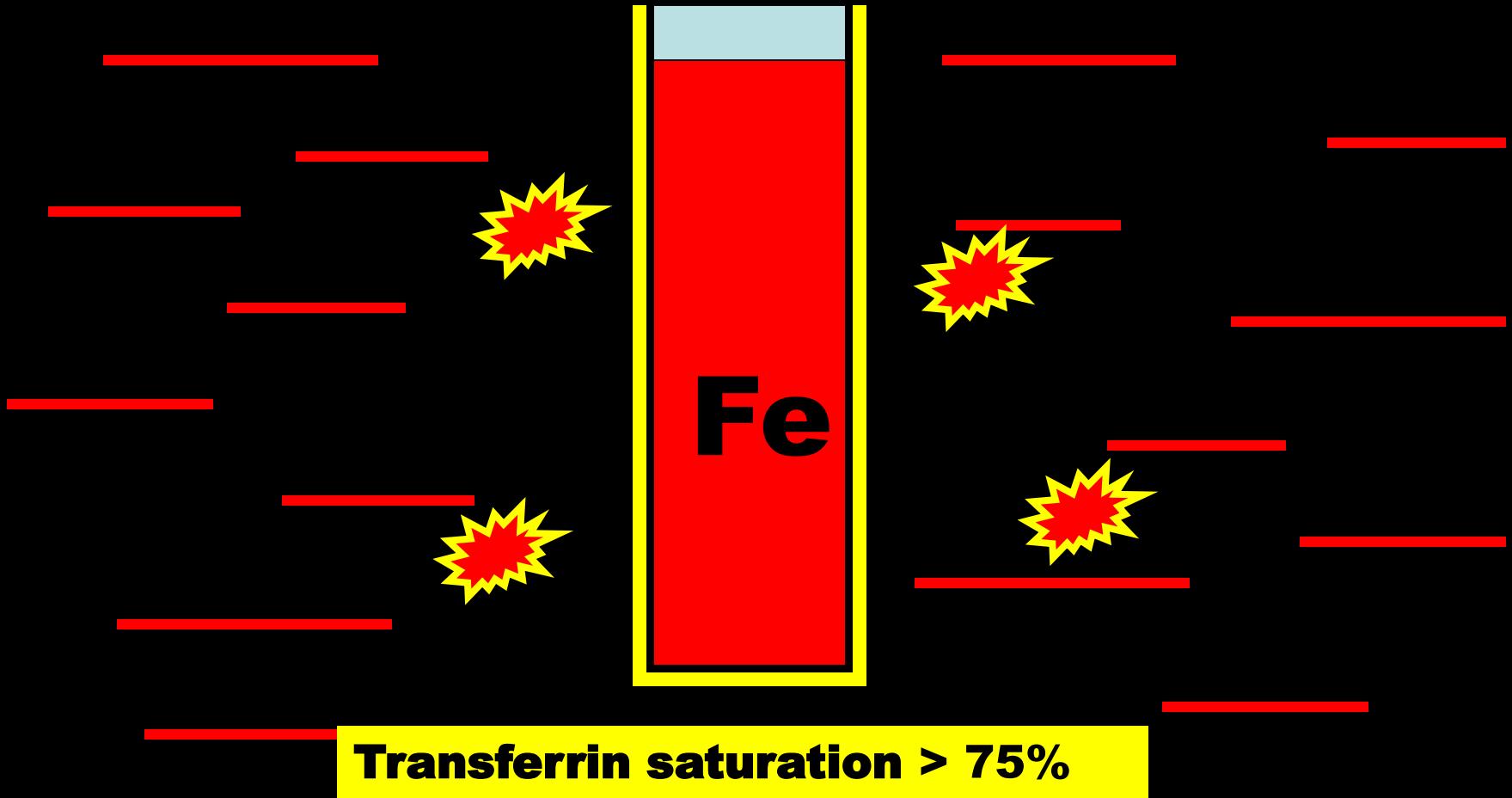
**Transferrin saturation > 60%**



Fe



# LPI (Labile Plasma Iron)

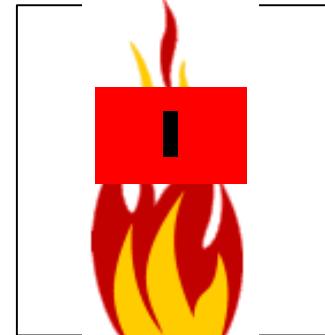




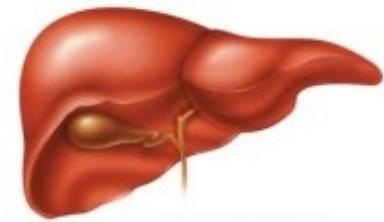
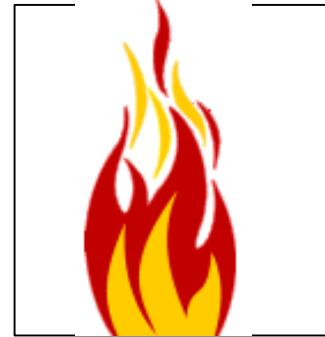
Ferritin



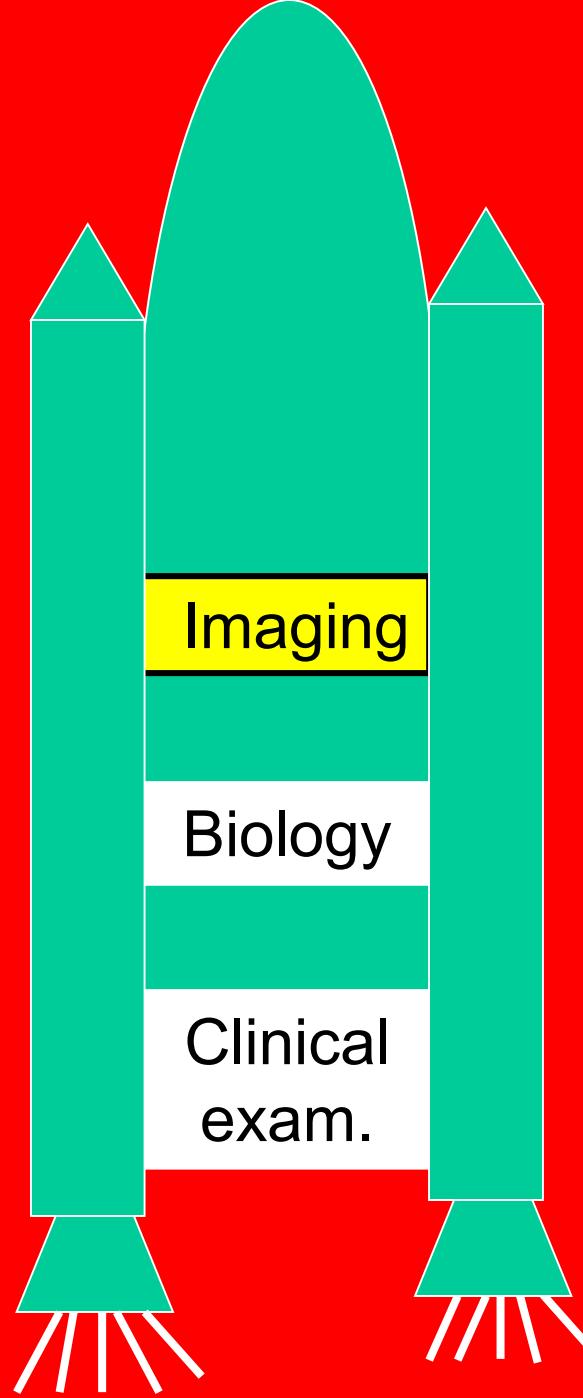
**Ferritin**



Ferritin



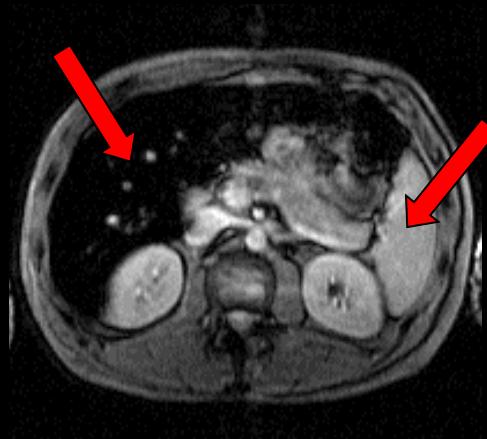
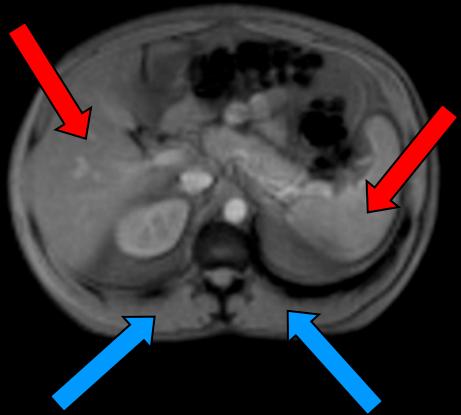
**Ferritin**





Hernando J Magn Reson Imaging 2014

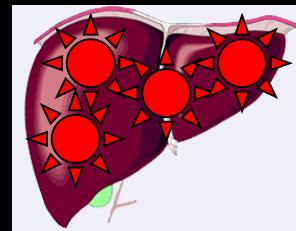
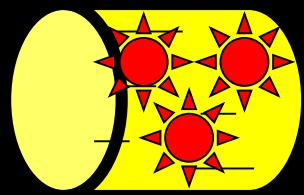
**black liver + white spleen**  
**=parenchymal iron overload**

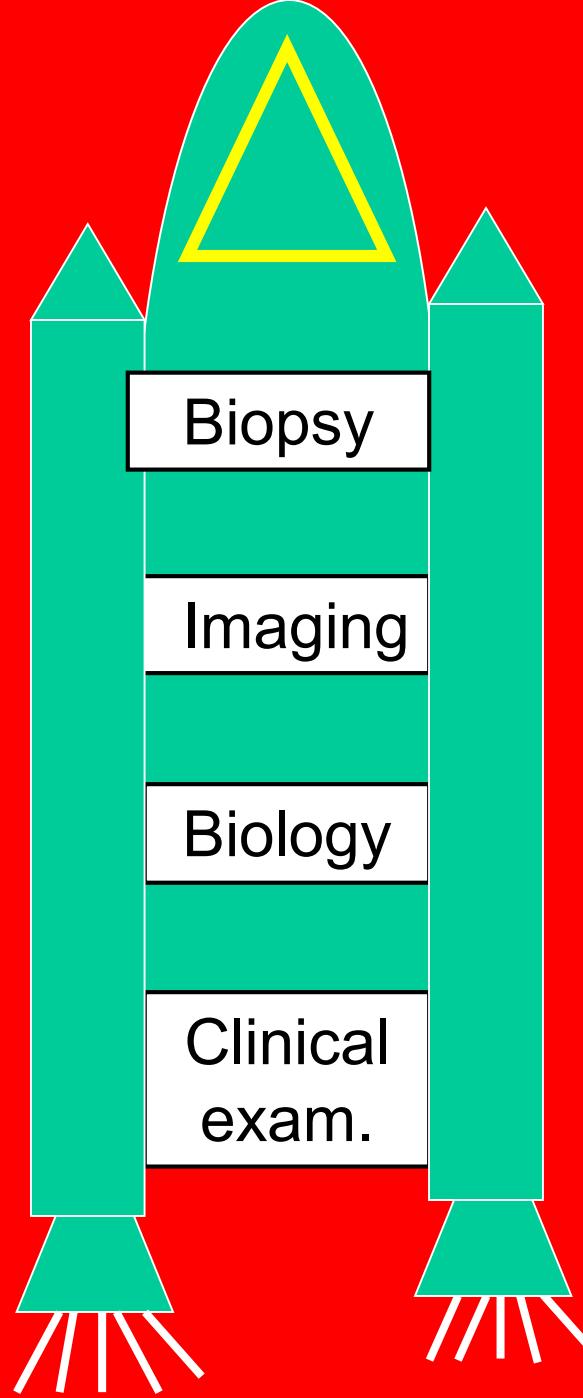


**black liver + black spleen**  
**=macrophagic iron overload**

([www.radio.univ-rennes1.fr](http://www.radio.univ-rennes1.fr))

Hernando J Magn Reson Imaging 2014

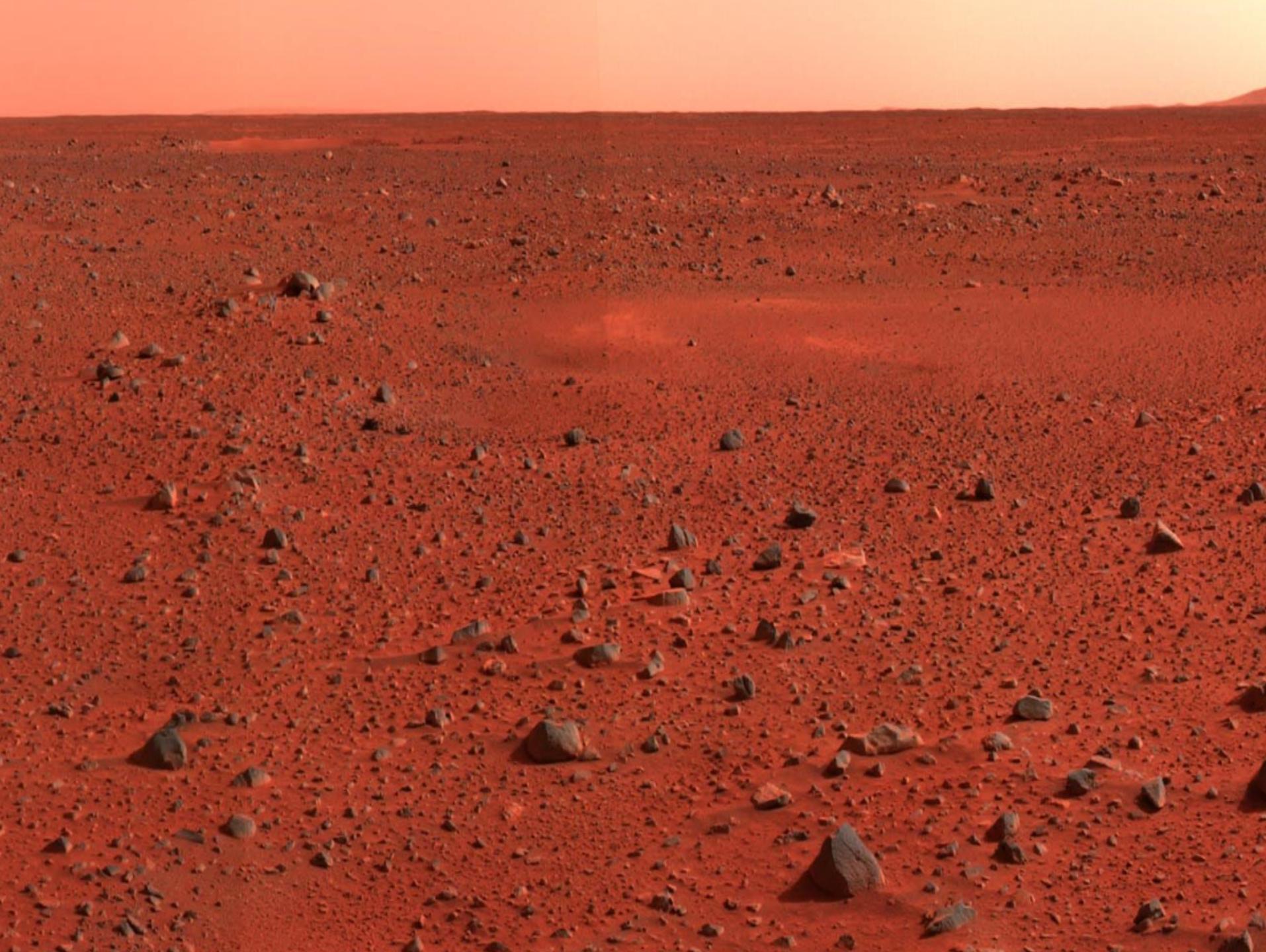


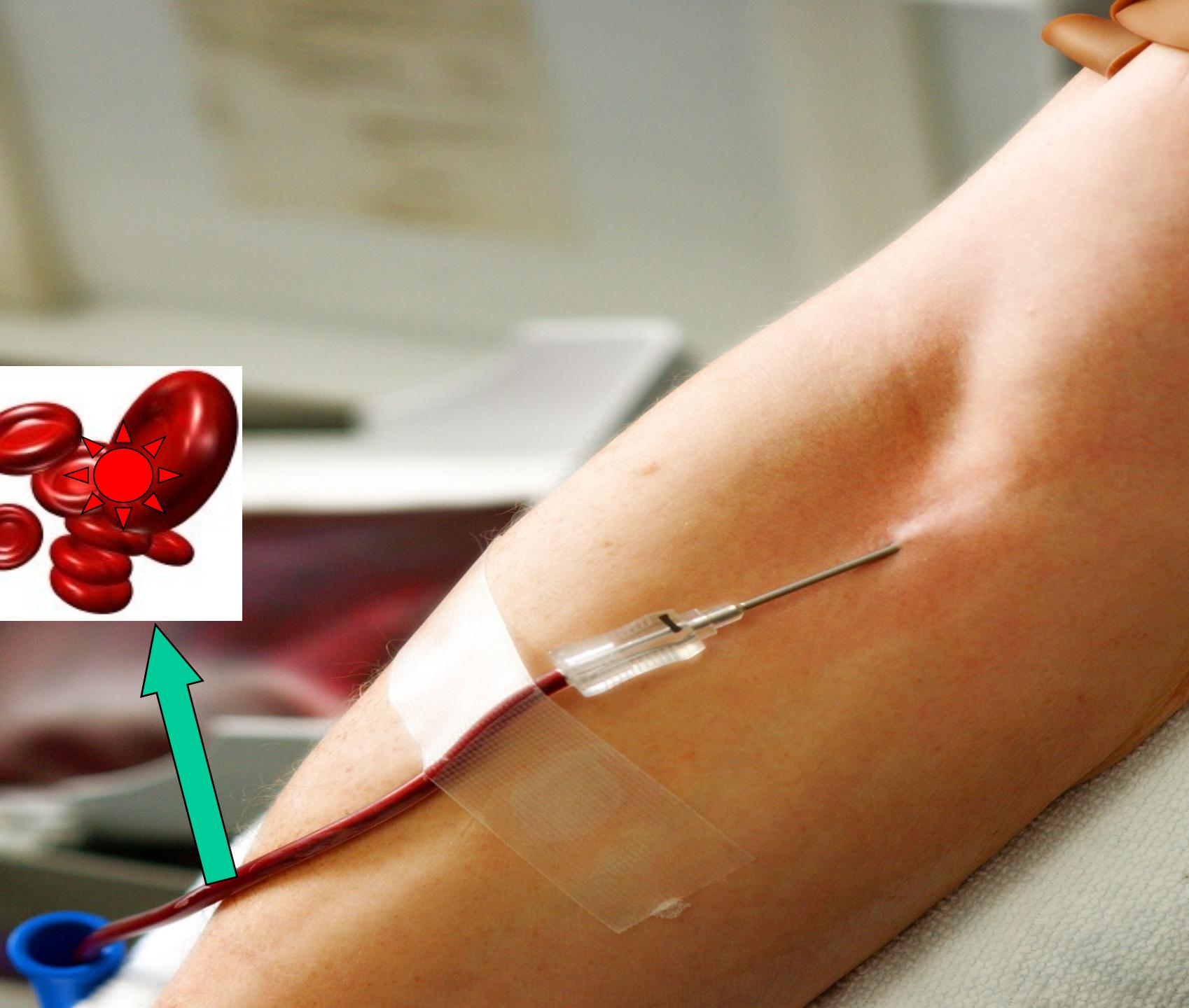
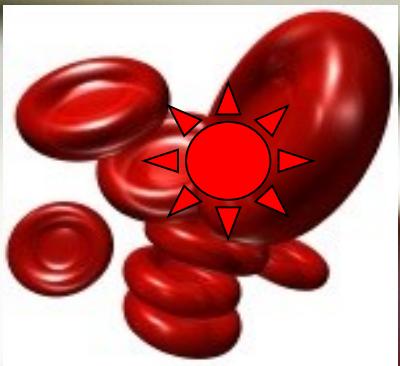


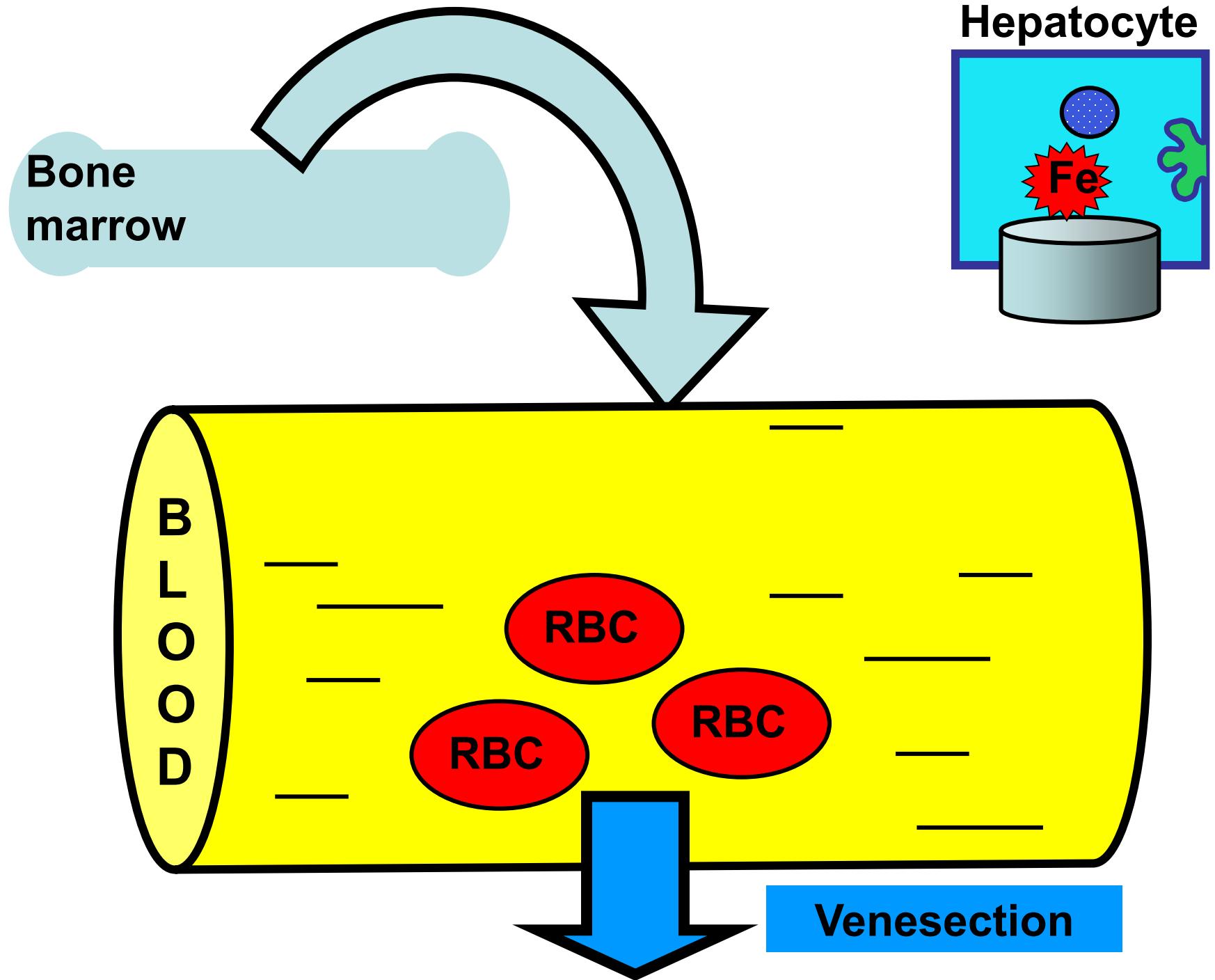
**Patho-physiology**

**Diagnosis**

**Treatment**







**FUTURE**

**Today**

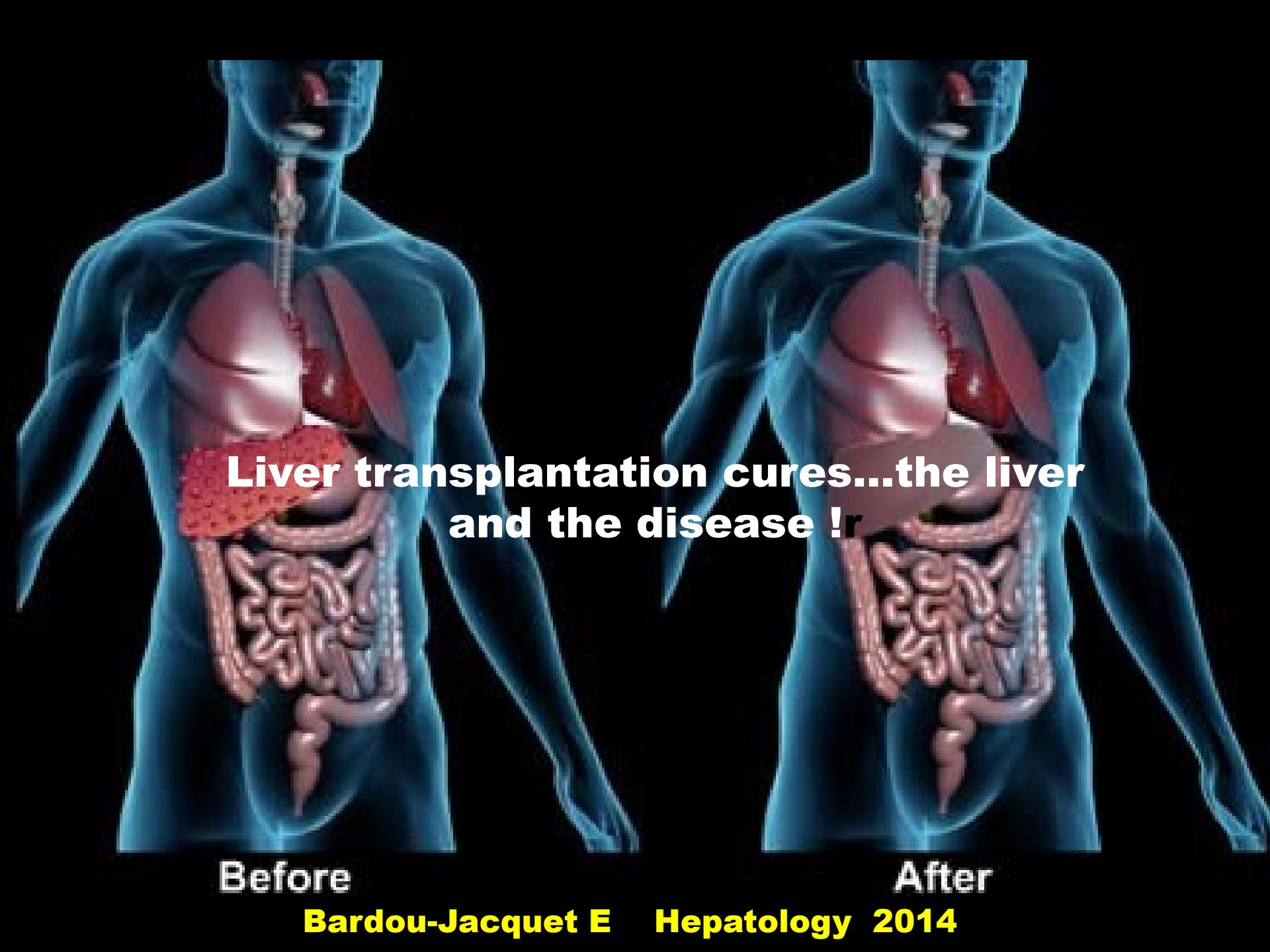
**Chelation**

# Deferasirox



**Tomorrow**

# **Hepcidin supplementation...**



**Liver transplantation cures...the liver  
and the disease !r**

**Before**

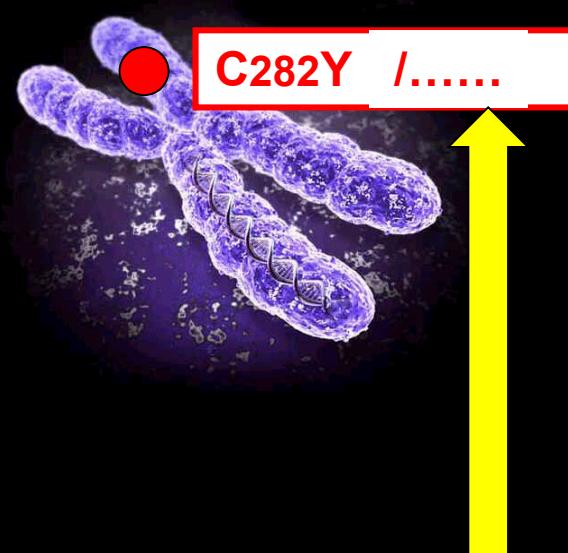
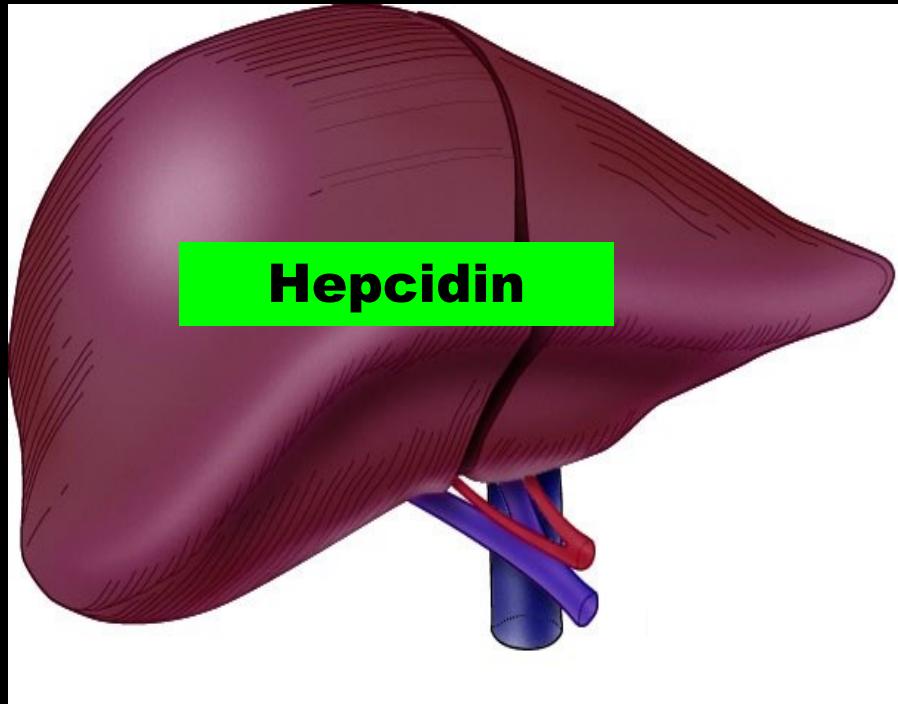
**After**



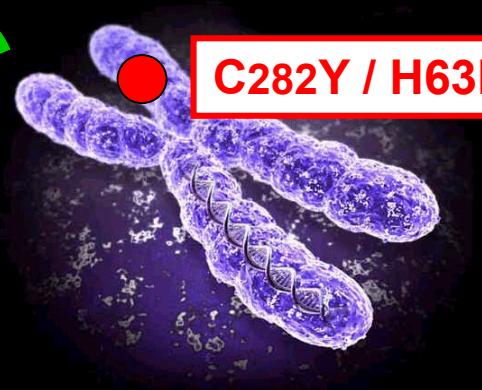
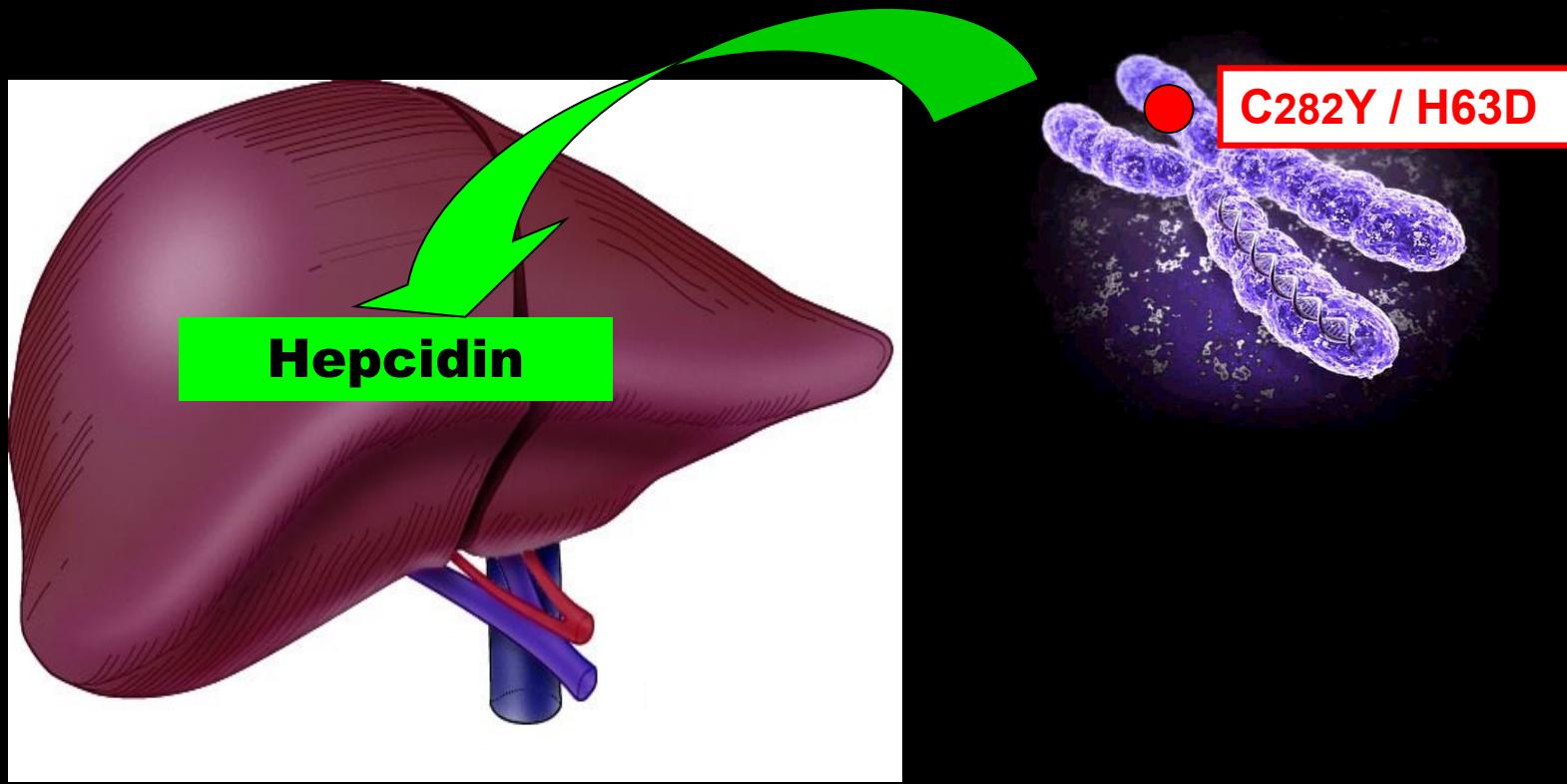
**HFE**

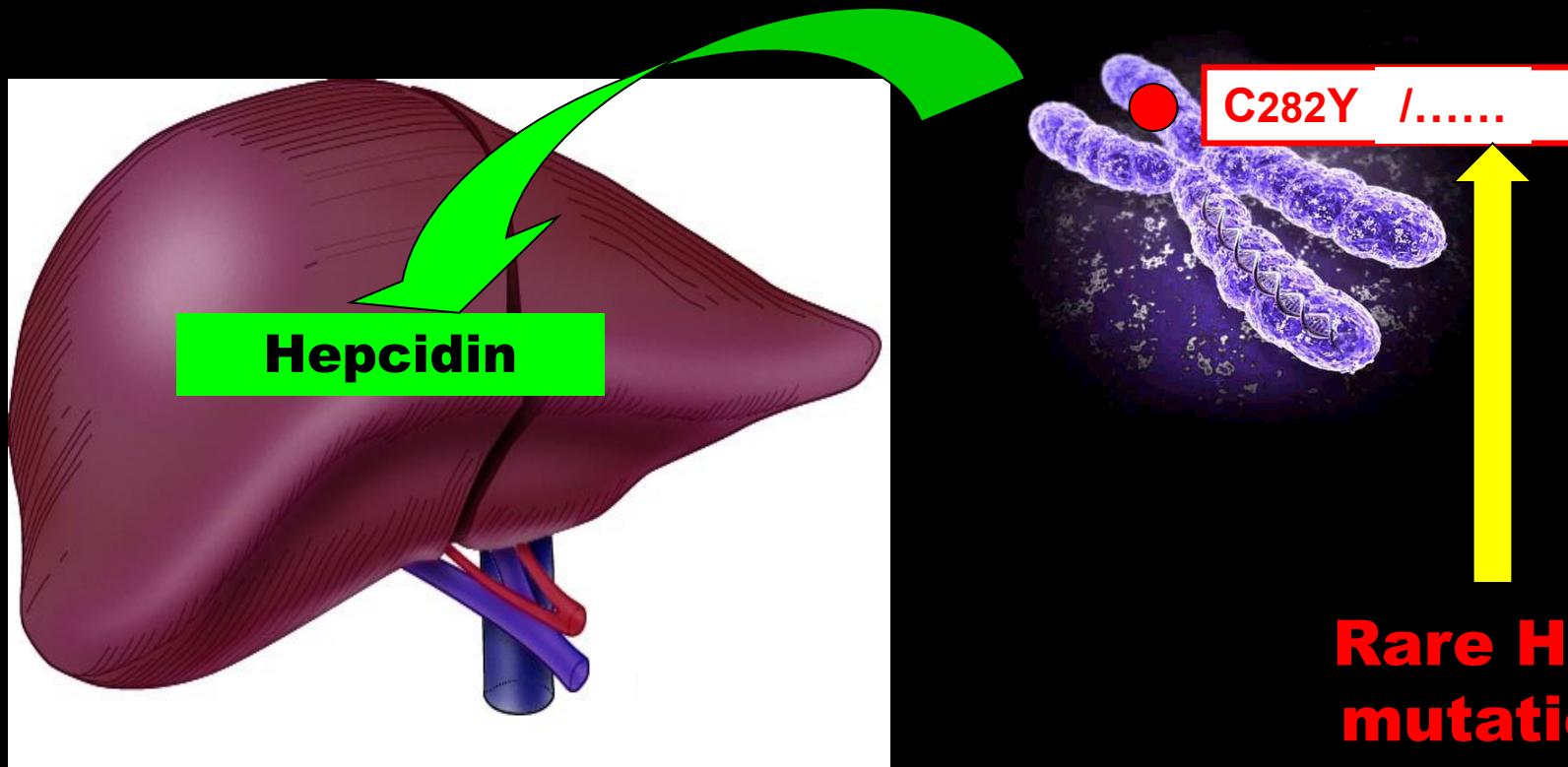
**HFE-related Haemochromatosis**

**C282Y/.....**



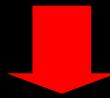
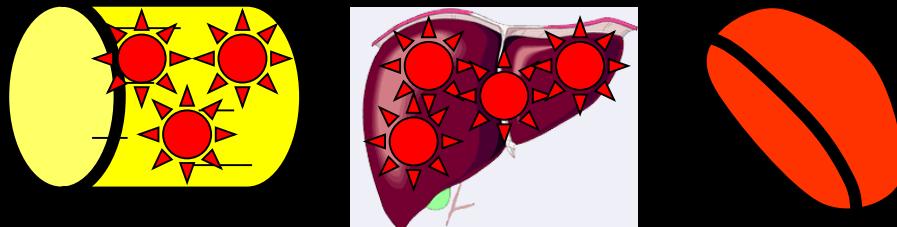
**Frequent HFE mutation**  
**H63D**





**Rare HFE  
mutation**

**C282Y/R226G  
(Cézard C  
Blood Cell Mol Dis  
2014)**



**Hepcidin deficiency**



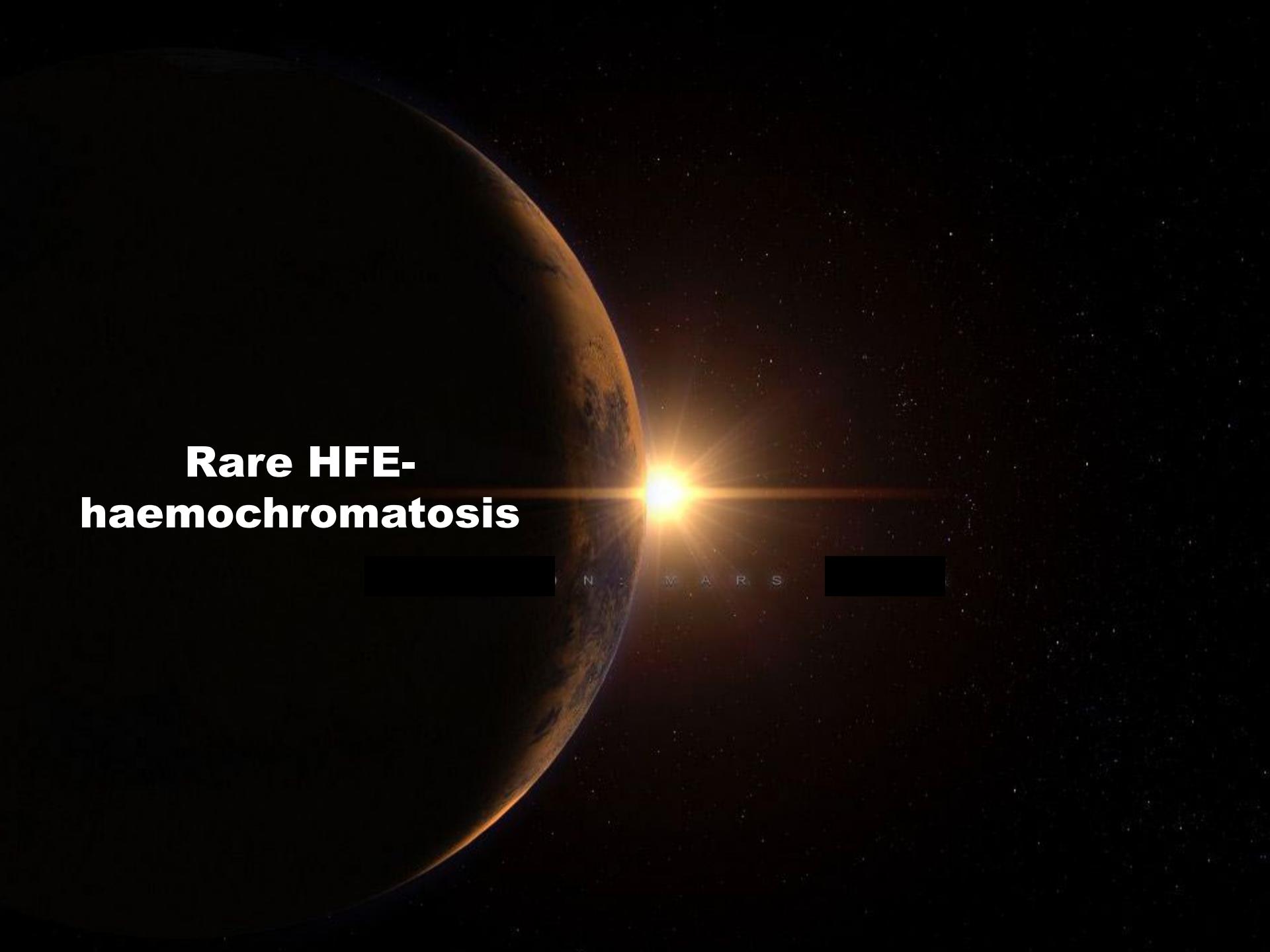
**«Classical» HFE-Haemochromatosis**

**(C282Y/C282Y)**



**Rare HFE-Haemochromatosis**

**(C282Y/rare mutation)**



# Rare HFE- haemochromatosis

N MARS

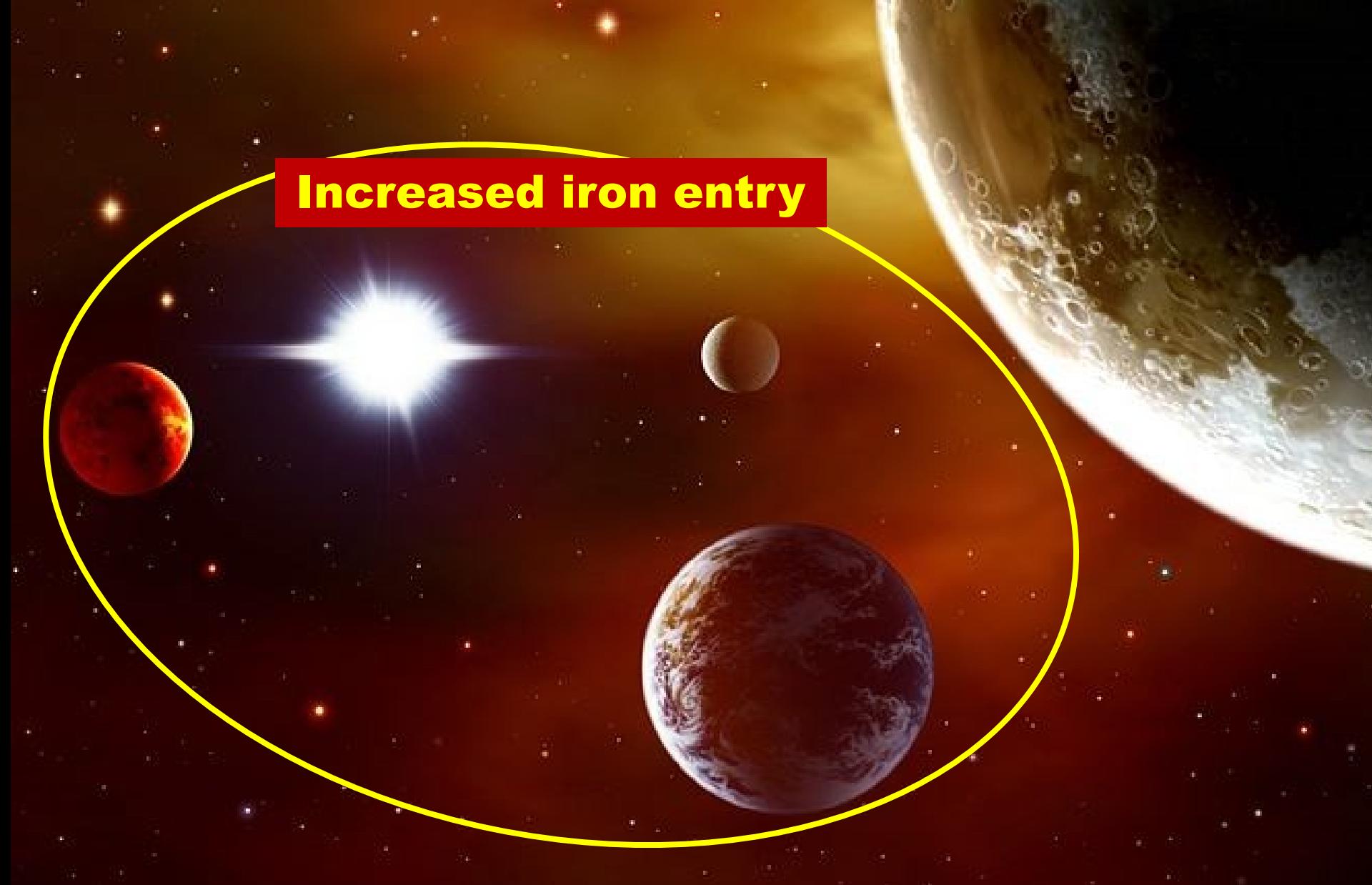




# **Non HFE-related Haemochromatoses**

**Camaschella C Curr Opin Pediatr 2011**

**Pietrangelo A Semin Liver Dis 2011**



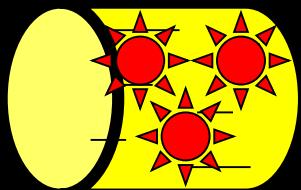
**Increased iron entry**

## Hepcidin deficiency

***HAMP***  
(hepcidin)

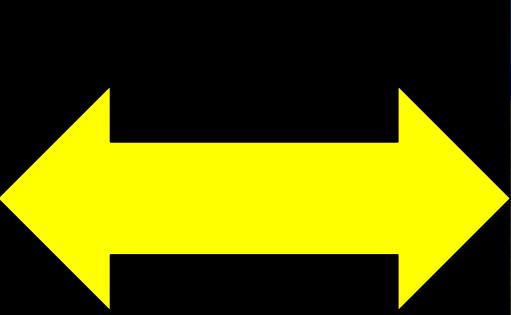
***TFR2***  
(transferrin  
receptor2)

***HJV***  
(hemojuvelin)



**<30years**





**Hepcidin  
supplementation...**

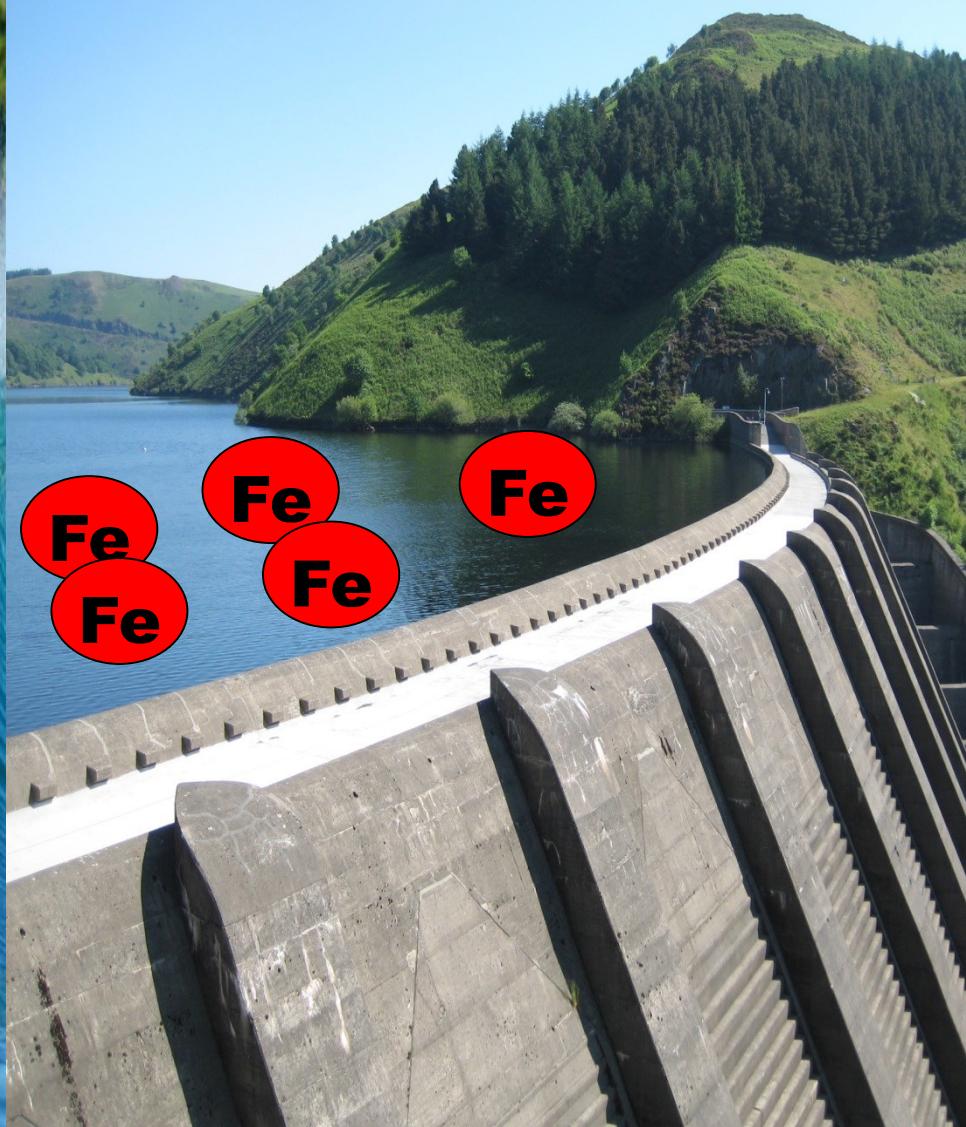
**Increased iron entry**

**HAMP**  
(hepcidin)

**TFR2**  
(transferrin  
receptor2)

**HJV**  
(hemojuvelin)

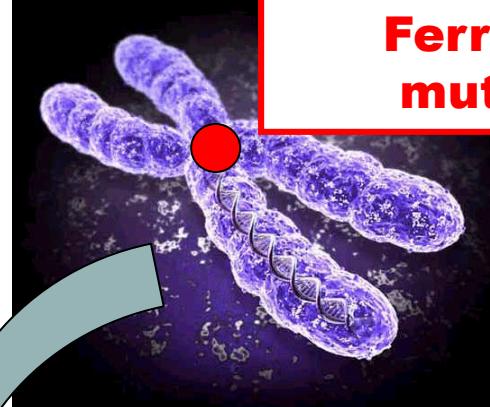
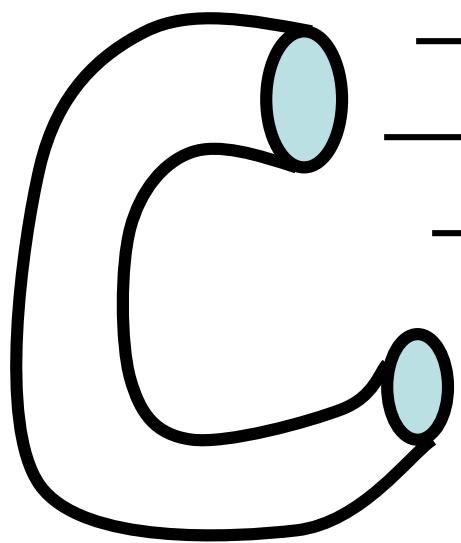
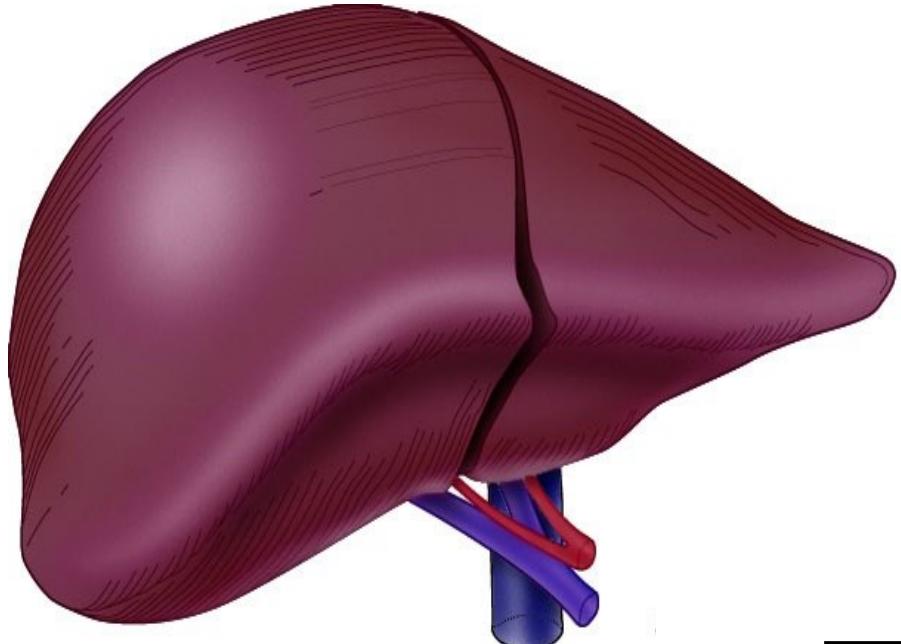
## Decreased iron exit



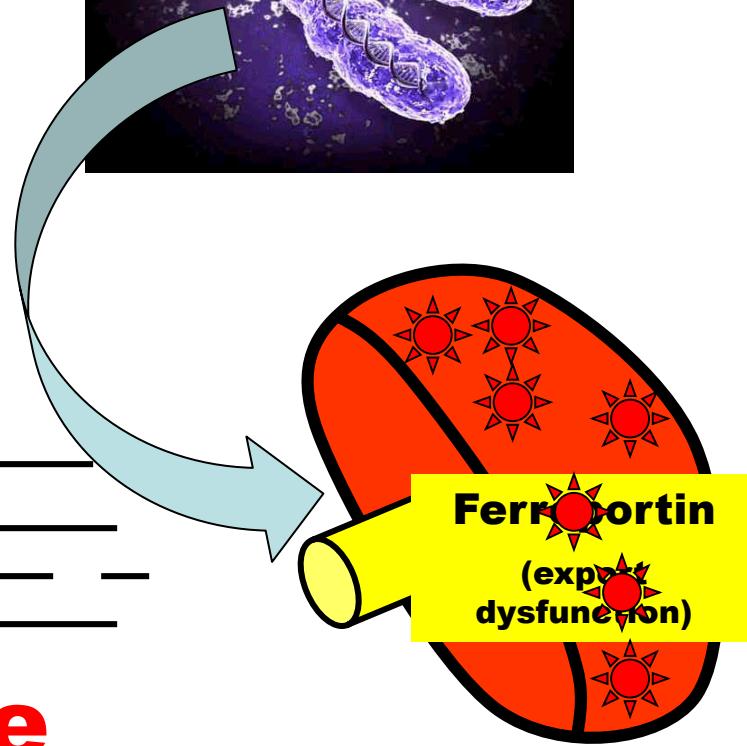


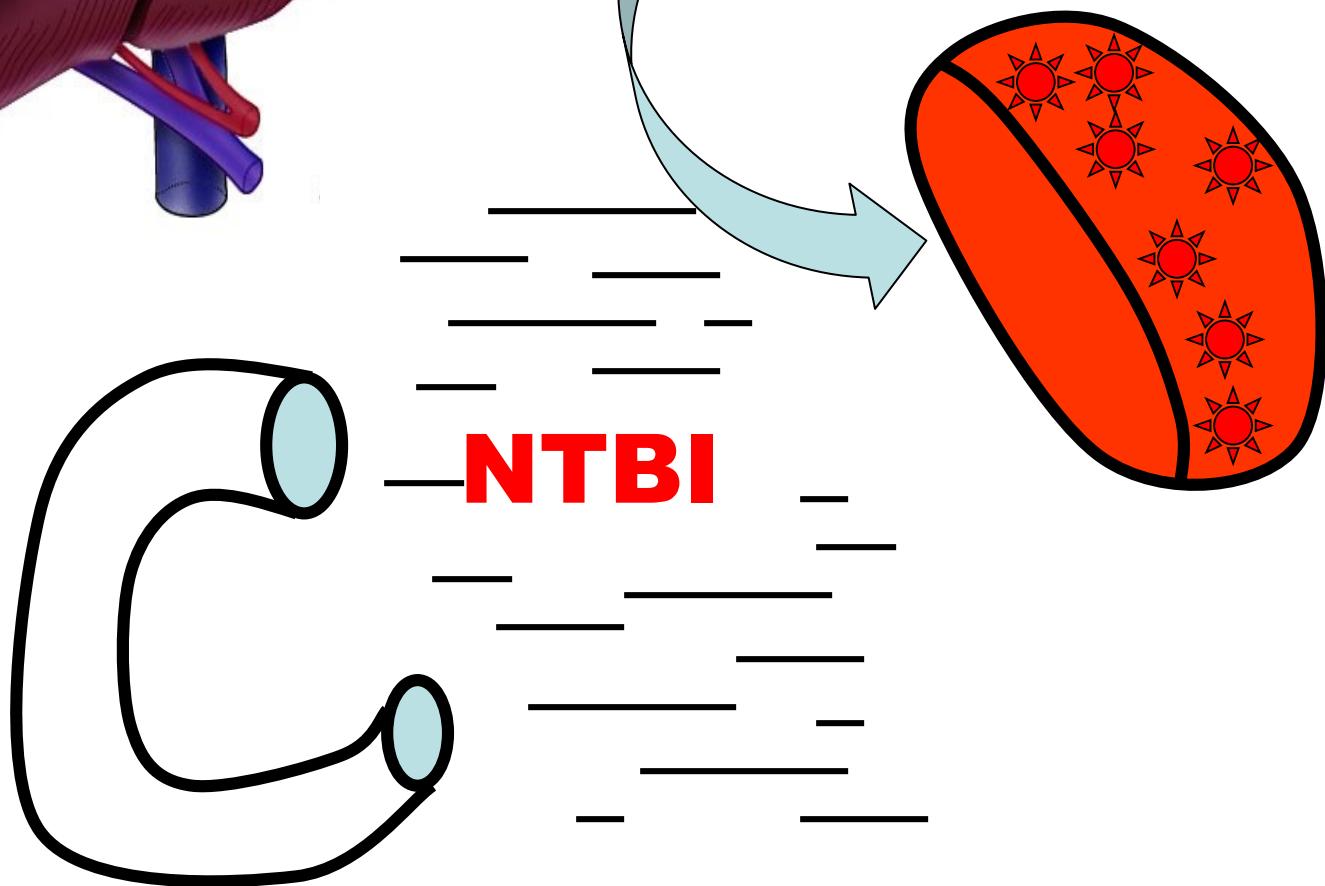
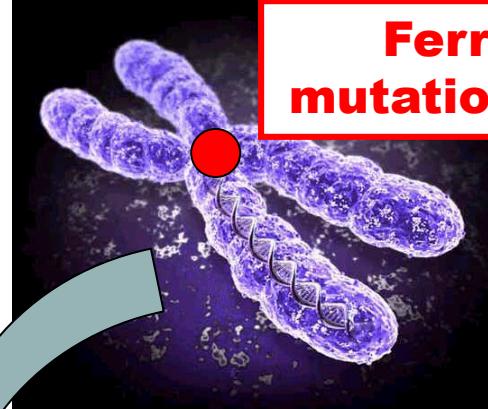
**Decreased iron exit**

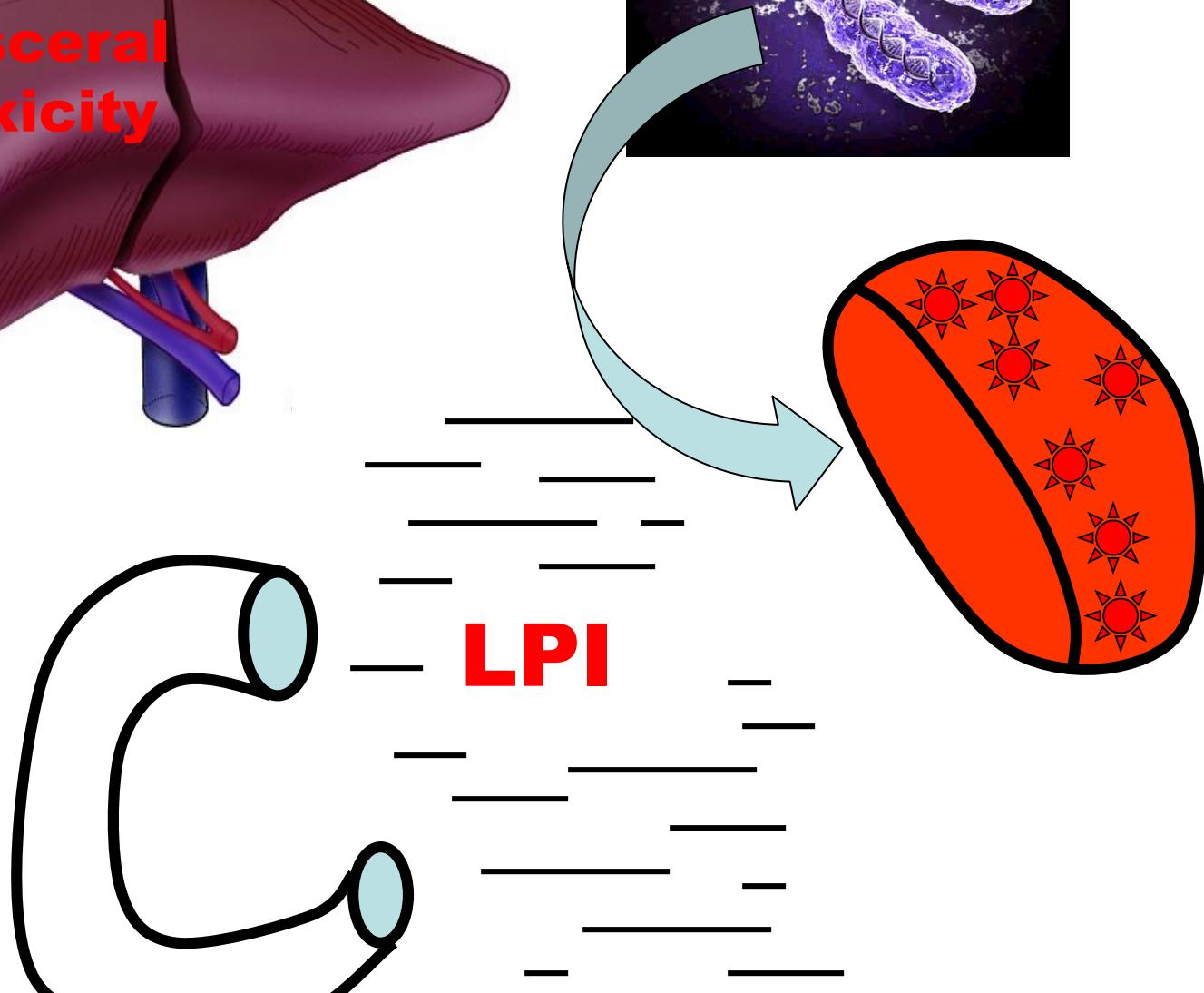
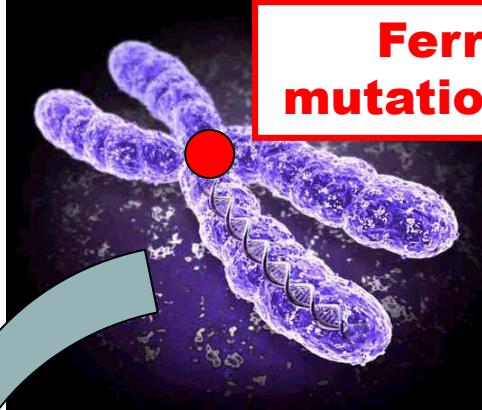
**Ferroportin disease**

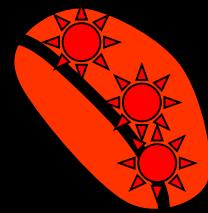
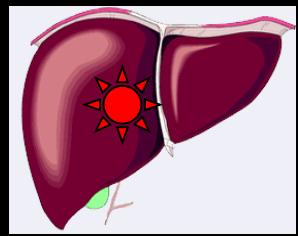
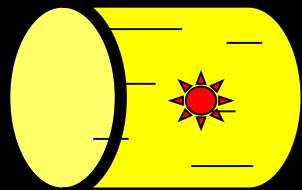


**Ferroportin  
mutations**



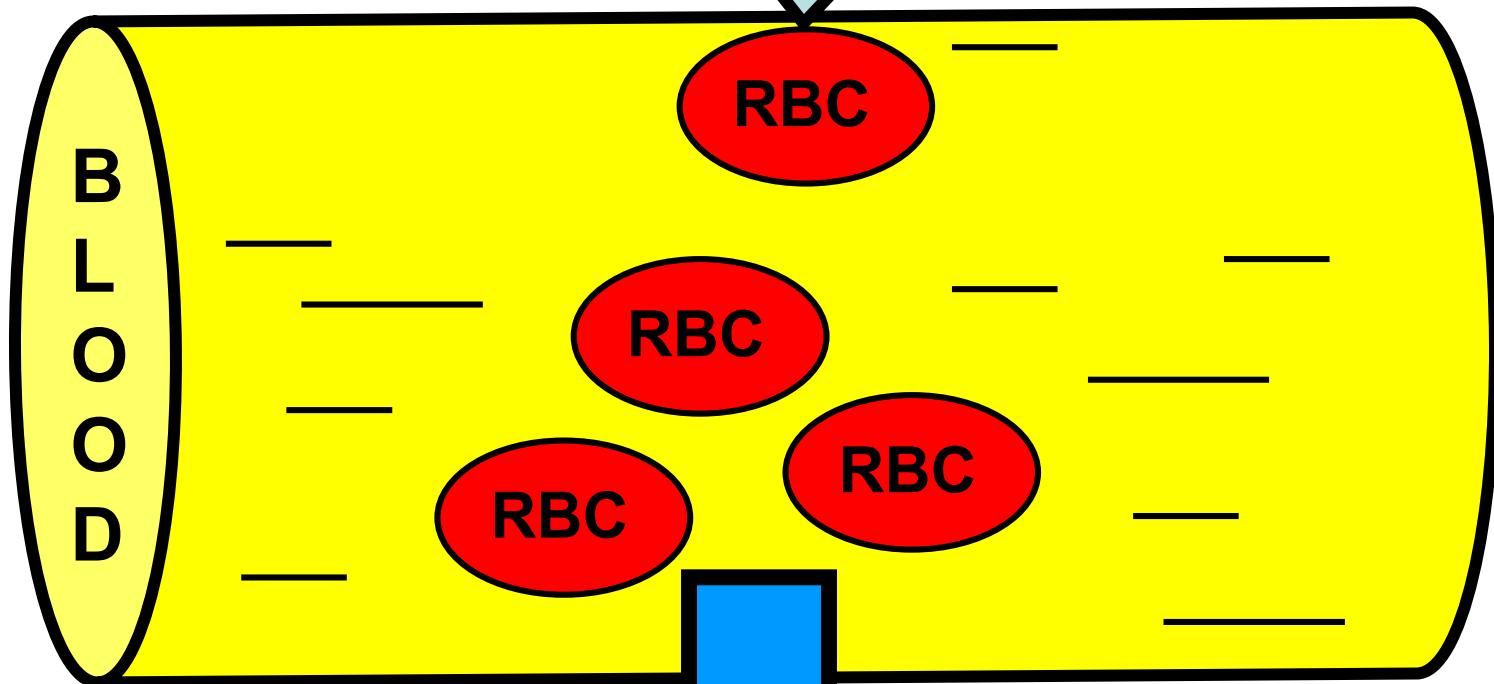
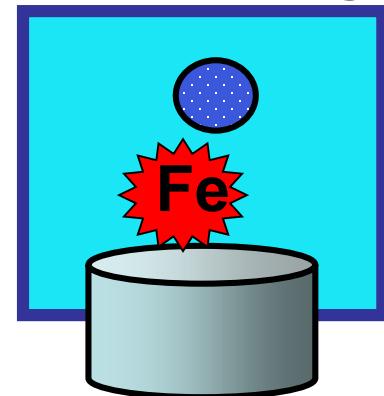






Macrophage

Bone marrow



**Decreased iron exit**

**Aceruloplasminemia**

**Anemia**

**↑ ferritin**



**Chelation**



TGTGGTGGCAAGGCCG



?



Fe

Fe