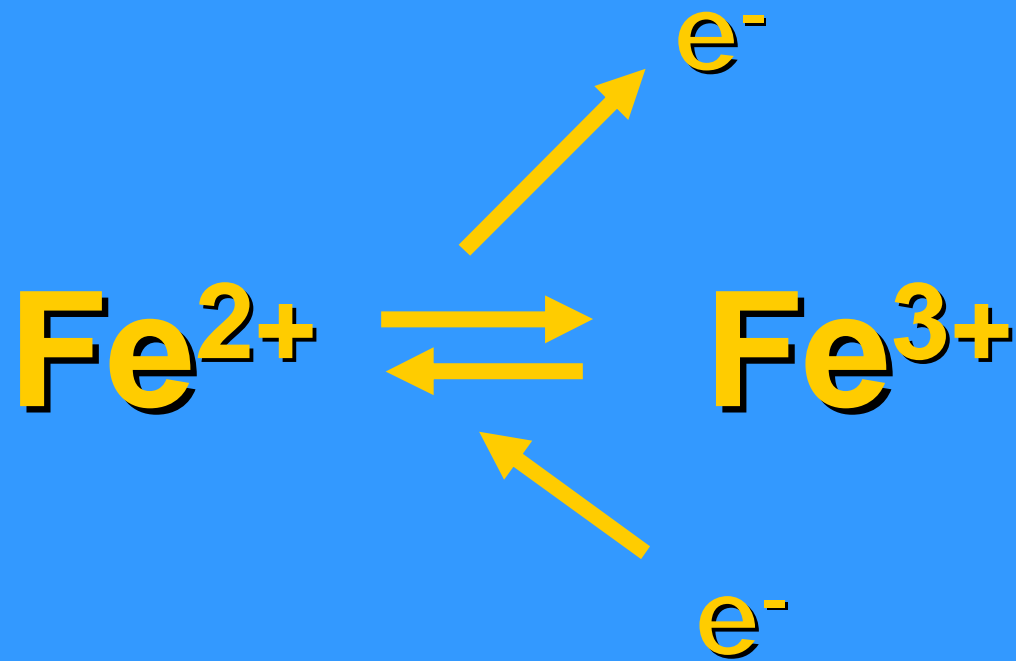


Hereditary Haemochromatosis (HH)

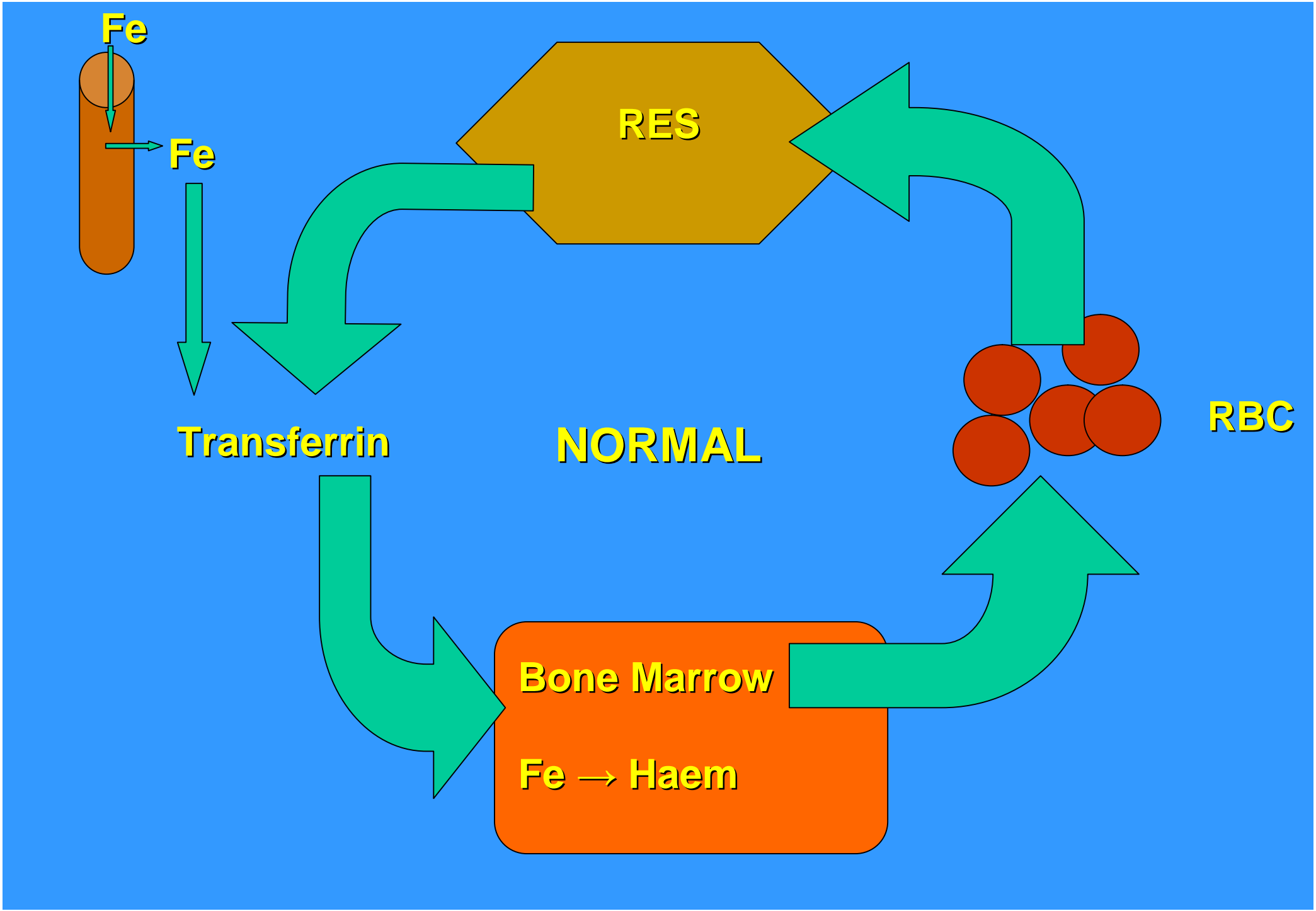
Address by Prof A P Mac Phail
At the Inaugural Meeting of the
Haemochromatosis Society of South Africa
1 November 2005

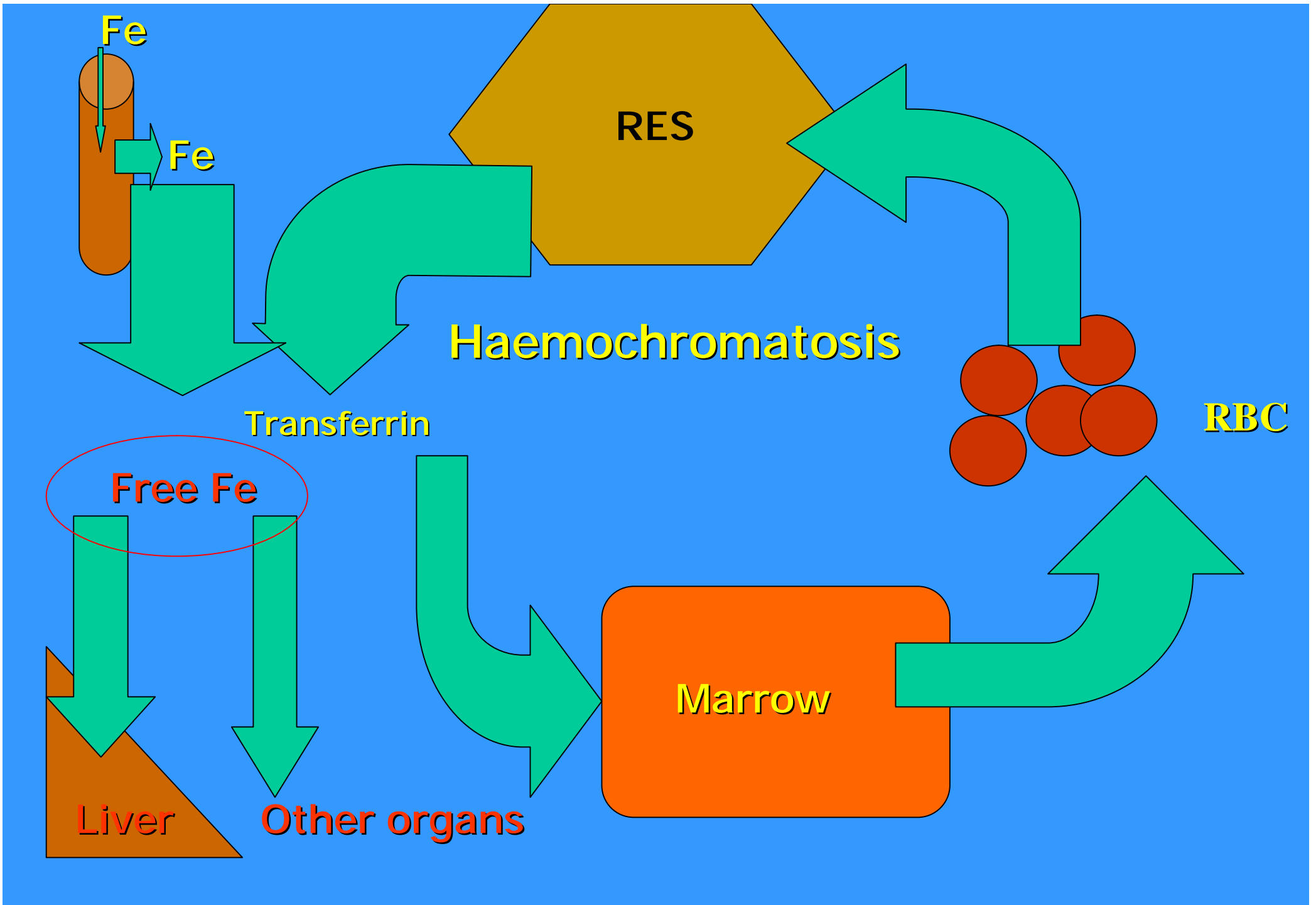
Iron is essential for life



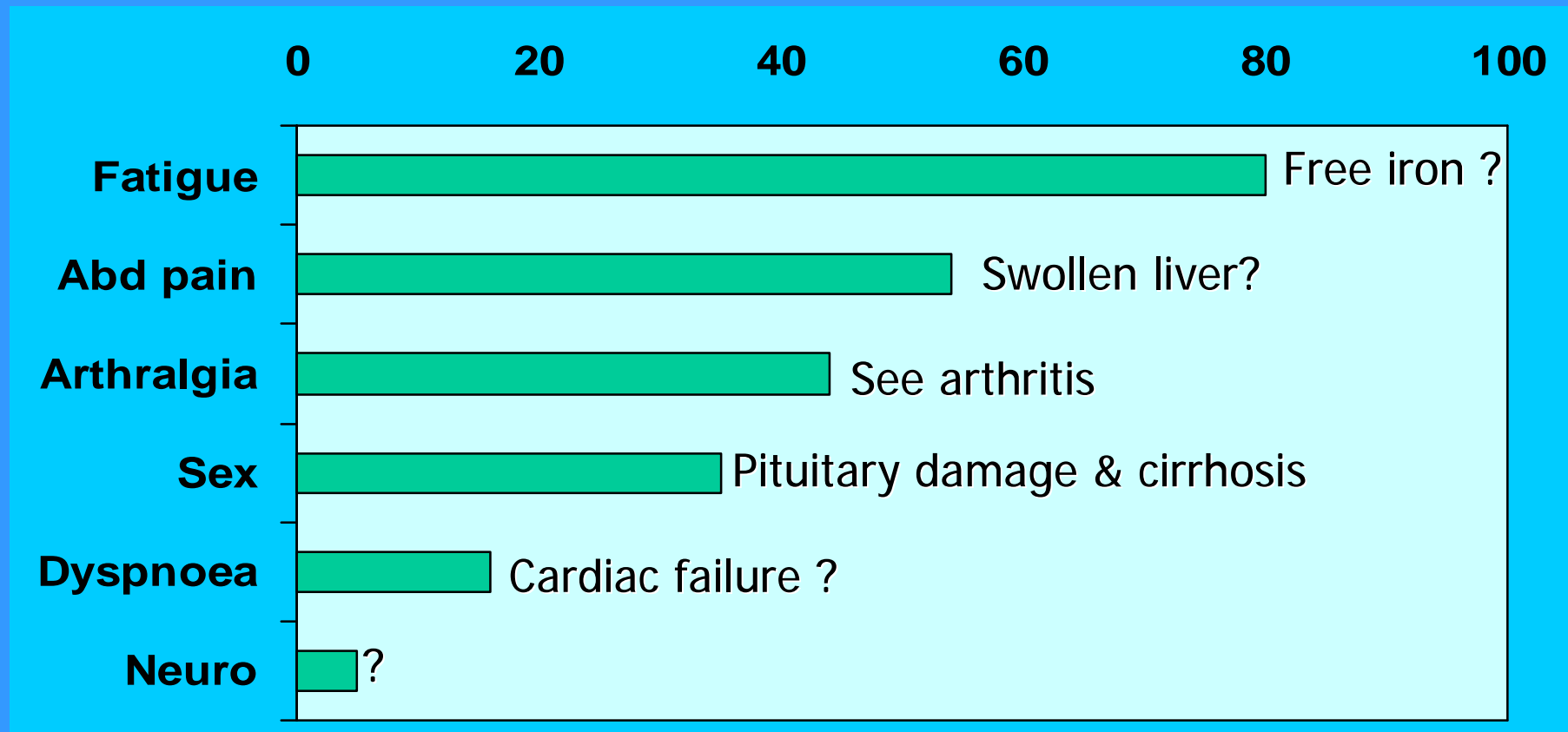
Too much iron is toxic

- Fenton chemistry
 - Production of free radicals
 - $\text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \text{OH}^- + \text{OH}^\bullet$
 - Damage to membranes and DNA
- Proteins of Iron Metabolism
 - Evolution of complex proteins
 - Make the most of iron's reactivity
 - Limit the damage

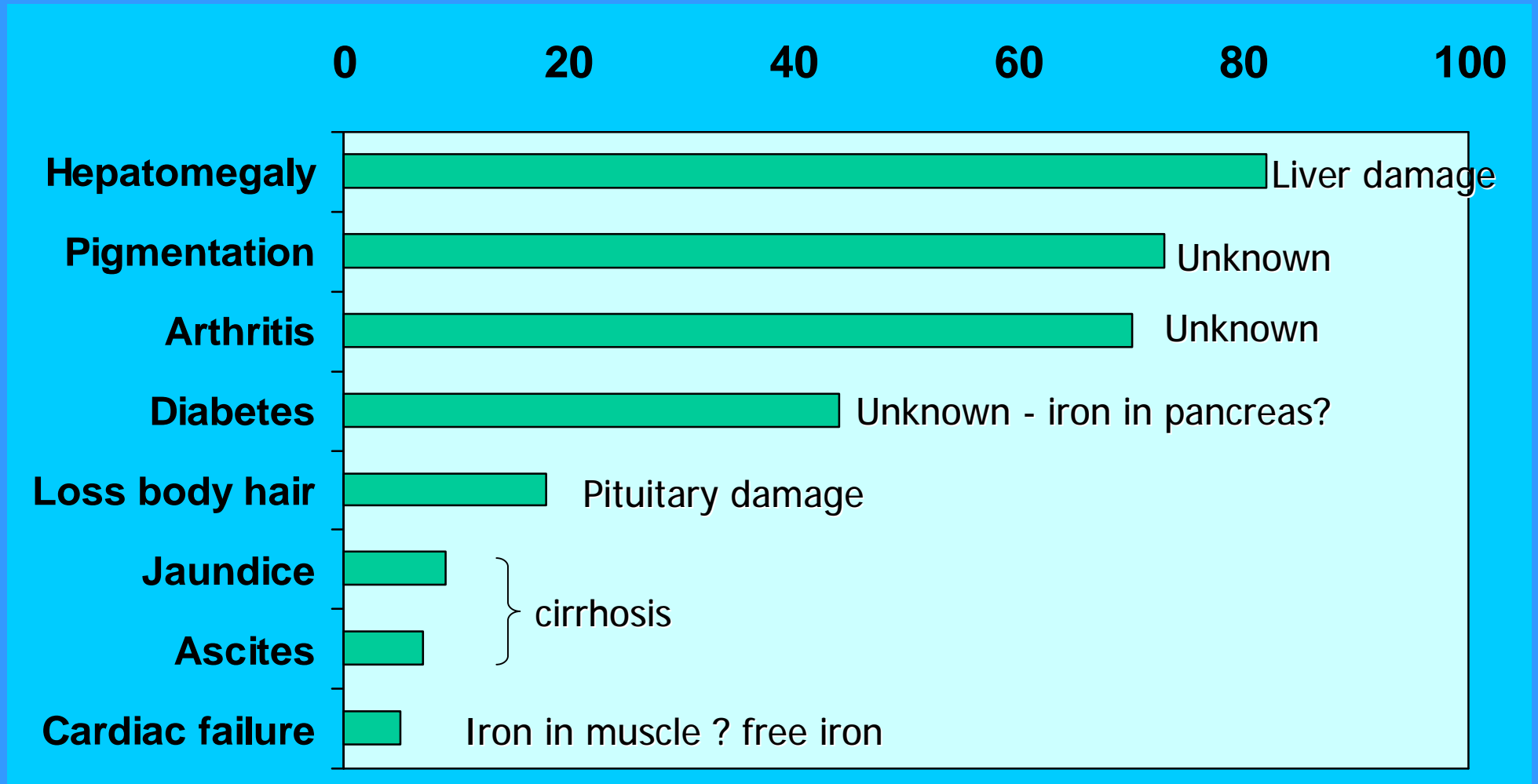




Symptoms of HH (circa 1990)



Signs of HH (circa 1990)



But many anomalies

- “Bronze diabetes” is rare
 - Severity of iron overload and diabetes don’t match
 - Pigmentation and skin iron don’t match
- Arthritis is not always prevented by de-ironing
- Severity does not match genotype
 - Most C282Y +/+ not iron overloaded
 - Some C282Y +/+ severe in second decade
 - Some severely iron overloaded are C282Y -/-
 - Some C282Y +/- severe

Milestones in the History of HH

- von Recklinghausen named it in 1895
- Sheldon's Classic Monograph 1935
- MacDonald – “It's all due to alcohol” 1950
- Simon proved the genetic component 1977
 - Autosomal recessive
 - Ch 6 Celtic origin
- Feder *et al* discovered the *HFE* gene 1996
- Non-*HFE* haemochromatosis 1999 - 2005

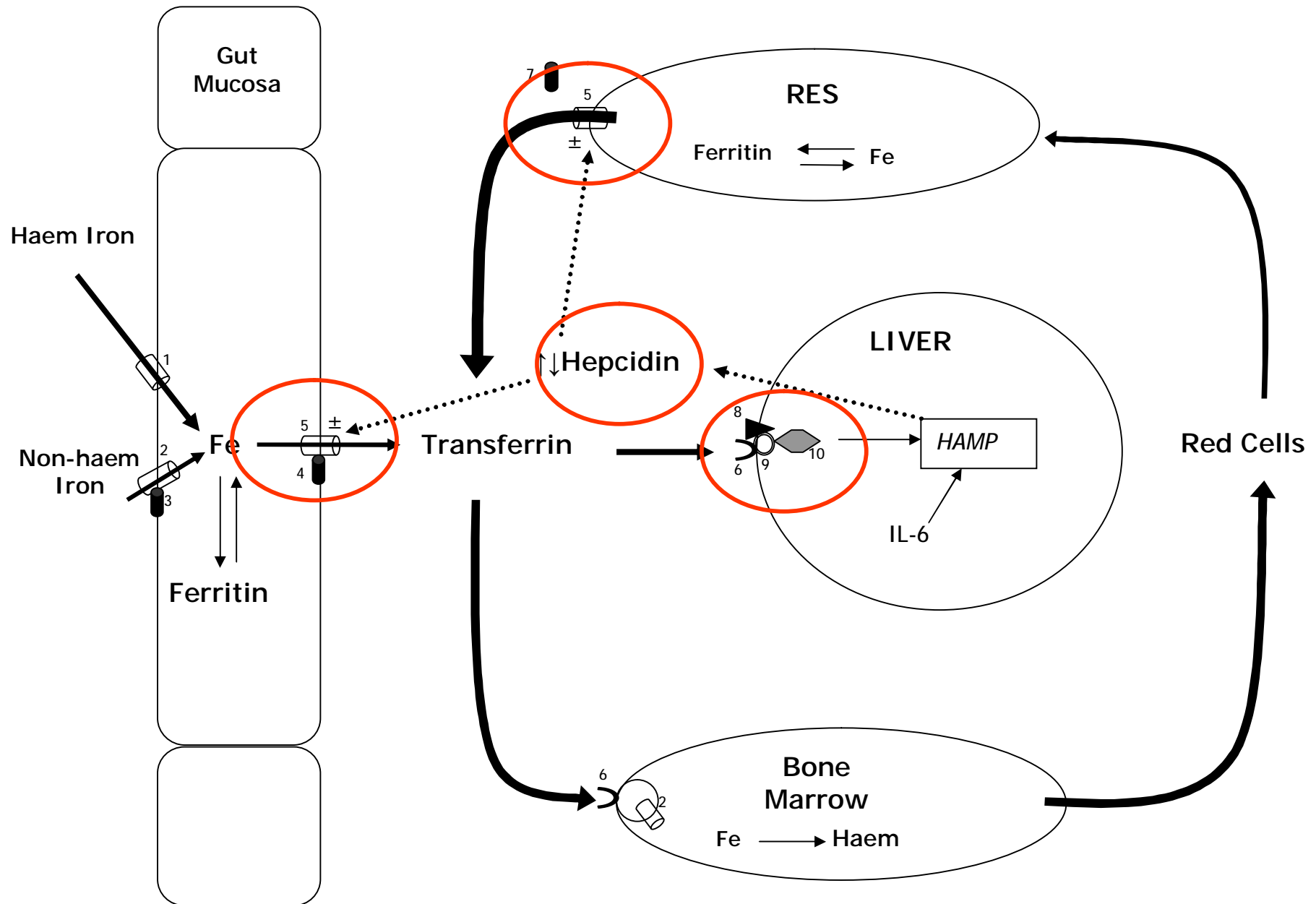
Genetic Haemochromatosis: Types 1 - 4

Type		Protein		Clinical
1	Classic (adult)	HFE		Recessive (2 copies), Severe but variable, pattern of iron deposition excess iron in circulation → Saturated Tf → tissues (liver, heart etc) → High S Ferritin
2	Juvenile	A	Hemojuvelin	
		B	Hepcidin	
3	Non-HFE (adult)	TfR2		
4	Dominant	Ferroportin		Dominant (1 copy), Very variable Loading of RES → High S Ferritin later → ↑ Tf-sat,

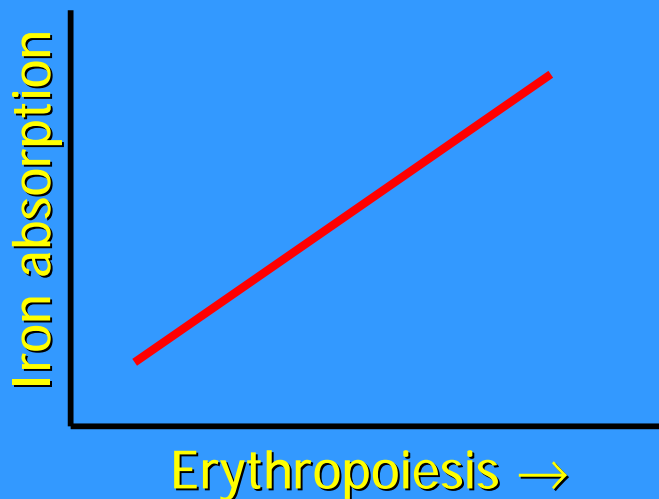
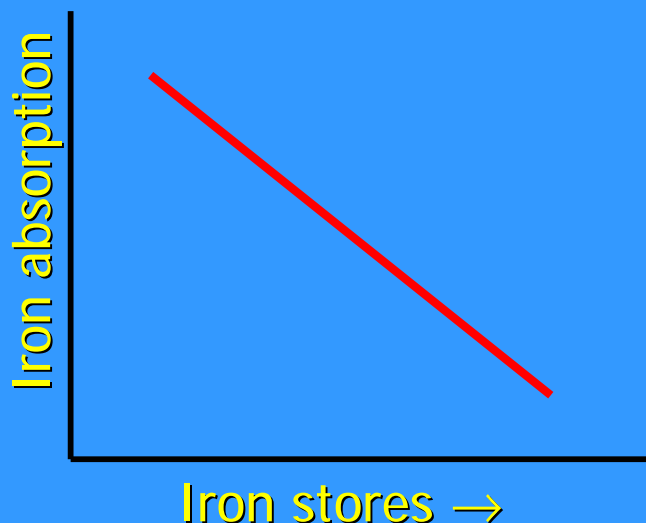
Liver: Central Controller of Iron Homeostasis

Role players

- HFE protein
 - Transferrin receptor 1 (TfR1)
 - Transferrin receptor 2 (TfR2)
 - Hemojuvelin
-
- Hepcidin → Ferroportin

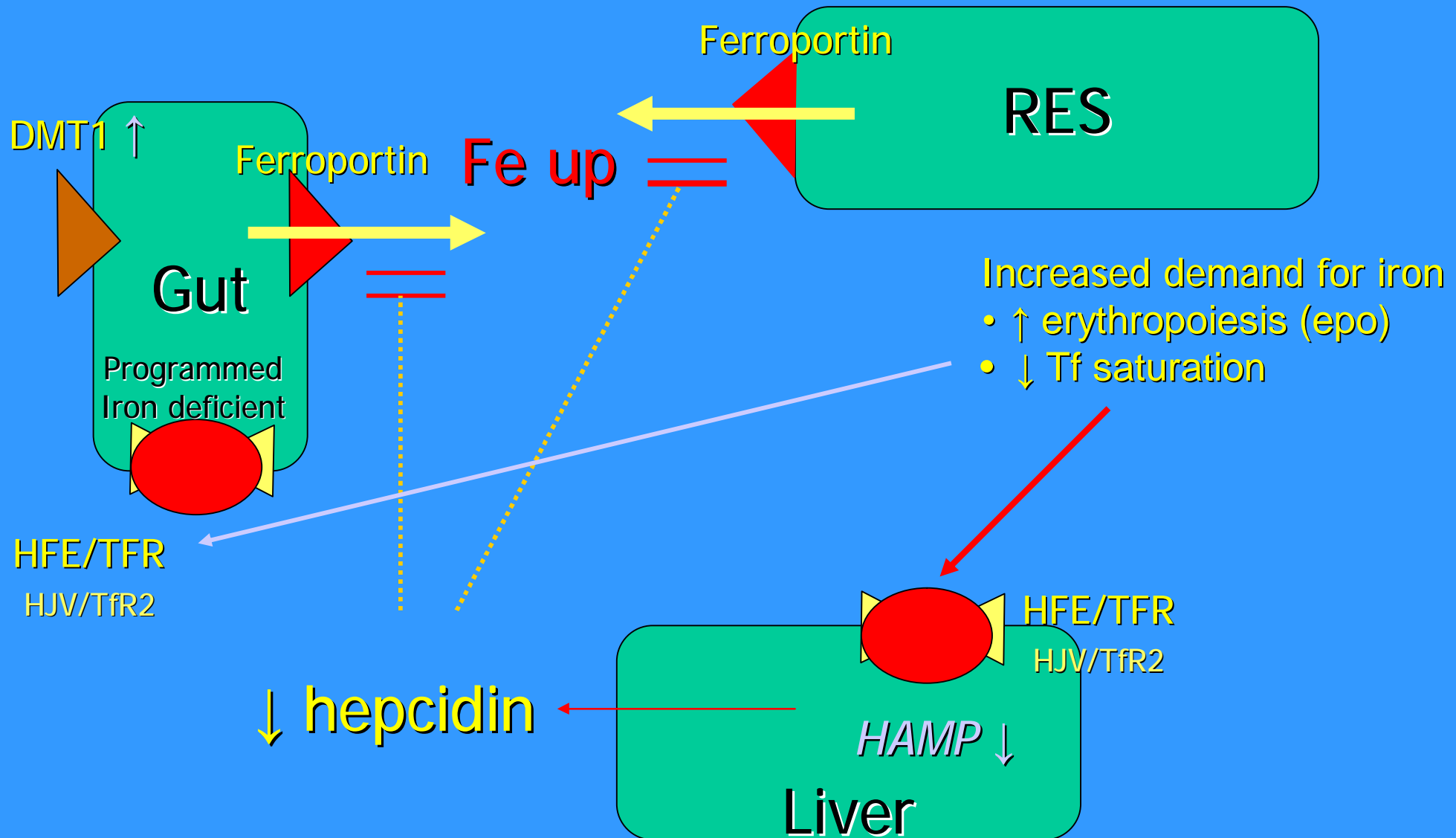


The Iron Regulator

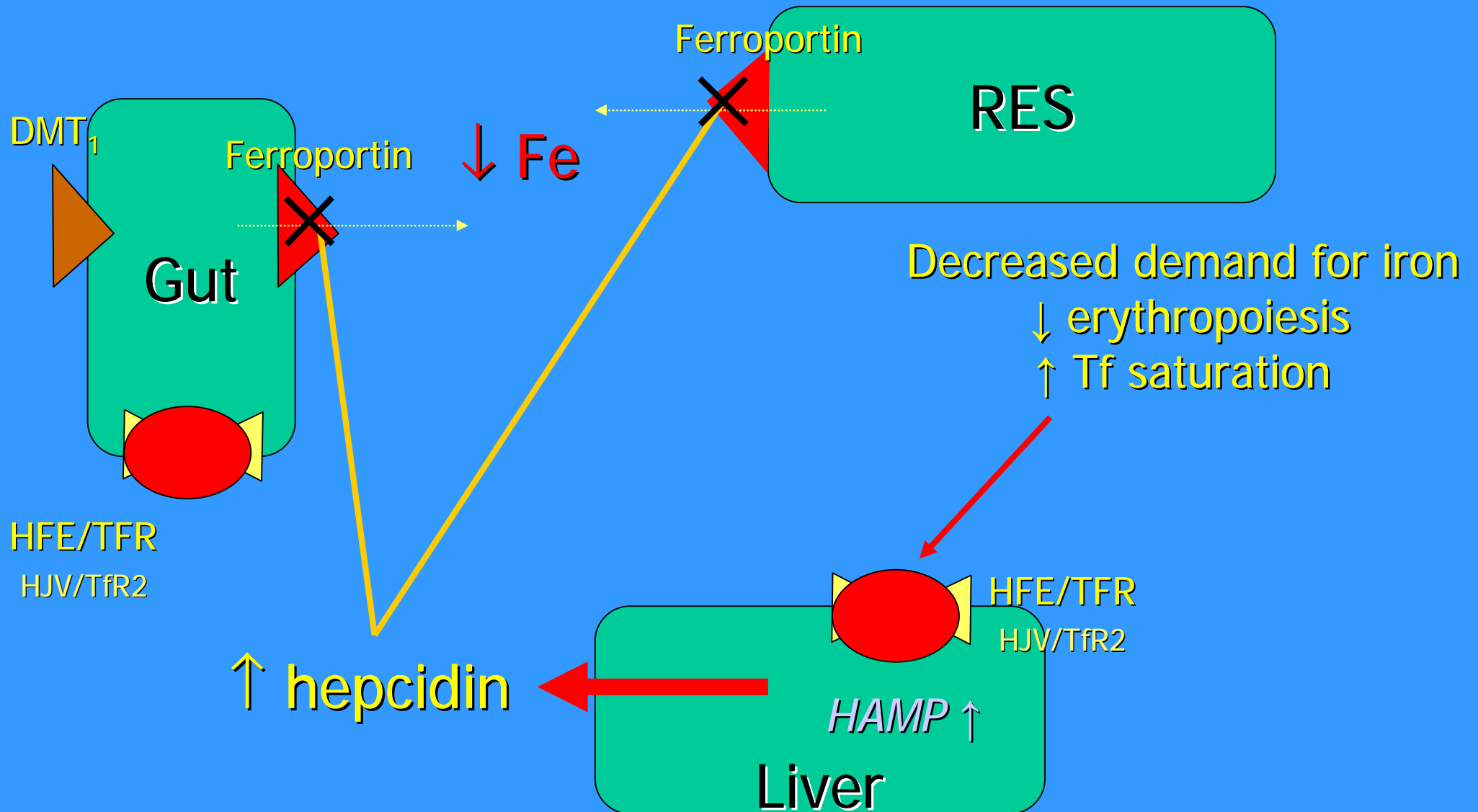


- Stores and Erythroid “Fermostat”
- Some circulating “factor” responsive to iron needs
- Hepcidin
 - Cationic polypeptide
 - Bacteriocidal properties
 - Synthesised in liver
 - ↓ iron deficiency & active epo
 - ↑ iron overload & inflammation
 - Cytokine dependent

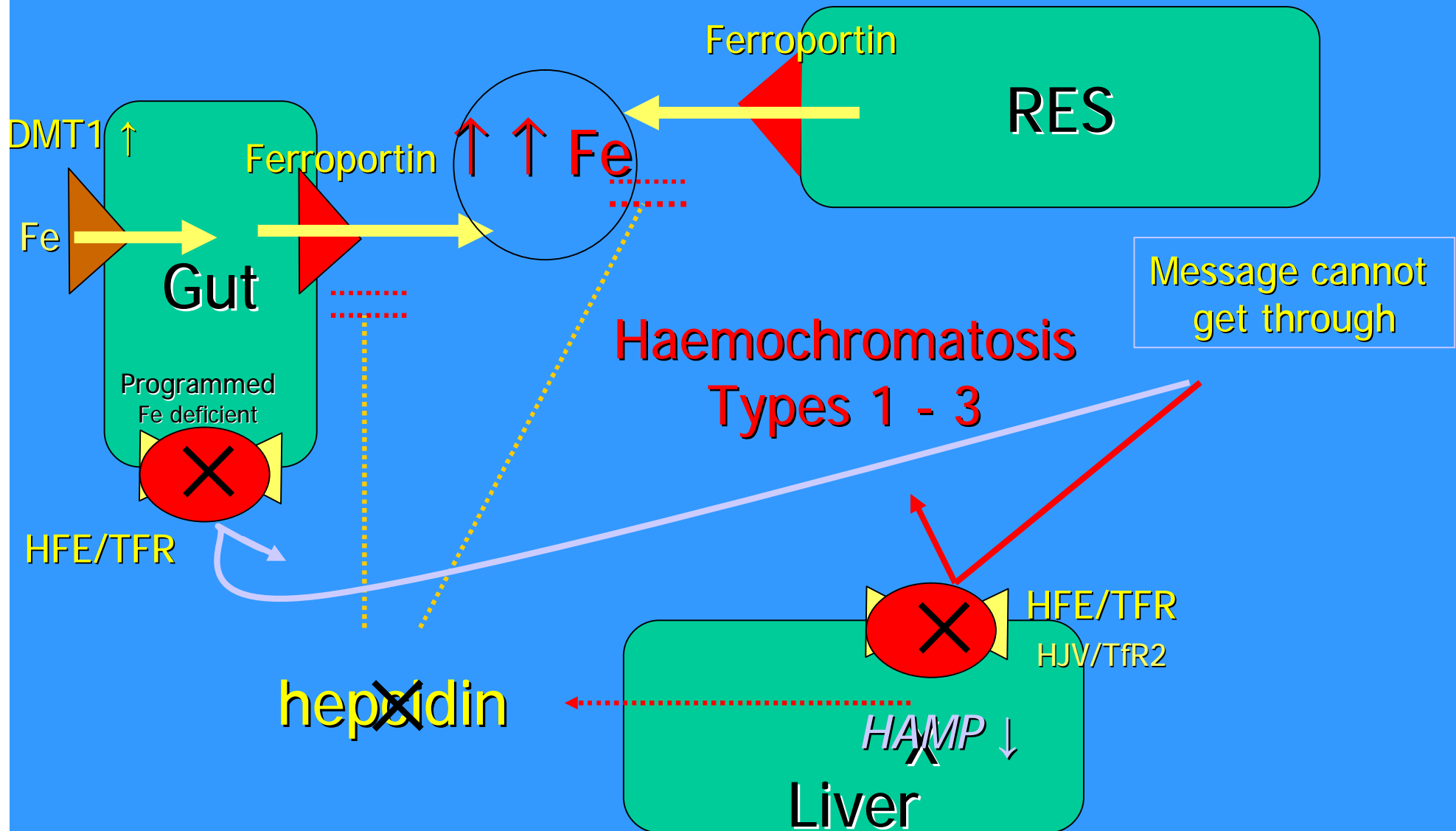
Hepcidin: The iron regulator



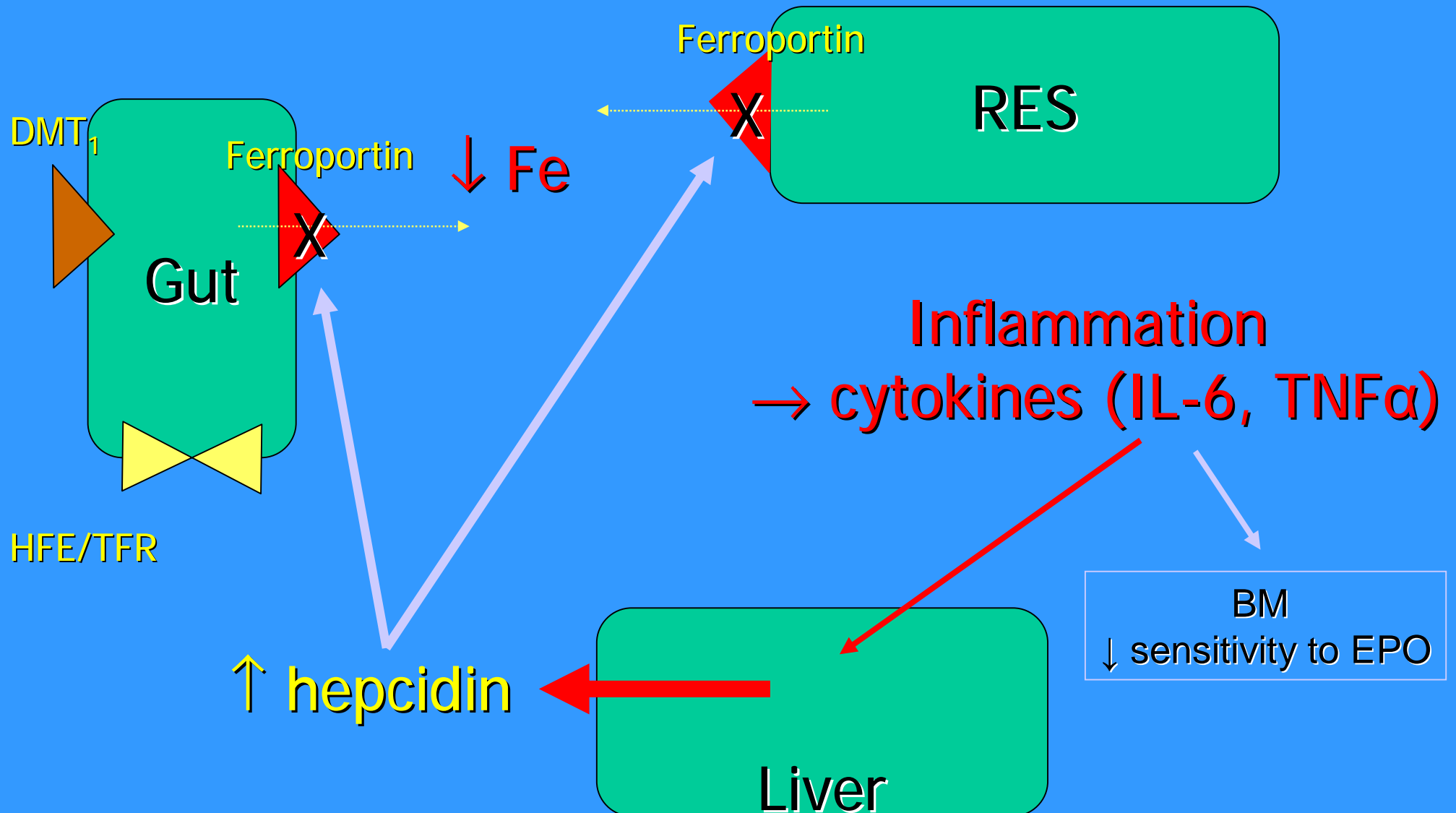
Hepcidin: The iron regulator



Hepcidin and Haemochromatosis



Hepcidin: Anaemia of Inflammation



HFE mutations and HH

HH Phenotype

- Homozygous
 - C282Y/C282Y (80%+)
 - H63D/H63D
- Compound heterozygous
 - C282Y/H63D, S65C, I105T, G93R, Splice
 - H63D/S65C

Mild iron overload

- Heterozygous
 - S282Y/wt

Prevalence of HFE mutations

Celtic origin of C282Y?

Irish	10% +/-	1.2% +/+
French	17% +/-	1.6% +/+
Caucasians	8 – 12% +/-	0.5% +/+

H63D more widespread

Caucasians	24% +/-	4% +/+
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Diagnosis of HH

- Clinical features
- High index of suspicion
- Transferrin saturation
 - >45% (F) >50% (M)
- Raised serum ferritin
 - 1 $\mu\text{g/l} \equiv 10 \text{ mg iron}$
- PCR for mutations of HFE gene
- Liver biopsy
 - No longer “gold standard”
 - cirrhosis / fibrosis
 - Hepatic iron index ($\mu\text{mol/g} \div \text{age}$)
 - MRI

Routine workup of HH

- Liver
 - Minimal changes on LFT
 - Fibrosis, cirrhosis, portal HT [sonar, biopsy]
 - HCC [sonar, α FP, Fe free foci]
- Endocrinopathy
 - Fasting serum glucose
 - Pituitary dysfunction [FSH, LH, TSH, ACTH]
- Cardiopathy
 - Echocardiography
 - ECG
- Arthropathy
 - X-ray [1, 2 MP joints]

Genetic Screening

- All siblings and parents of HH
- Offspring of HH
 - If spouse high risk origin
 - ? Transferrin saturation enough
- Population screening?
 - In high risk populations
 - Routine transferrin saturation

Treatment of HH

- **Phebotomy**
 - Aim: deplete iron stores
 - ↑ **blood production draws off iron**
 - Frequent [weekly @ 3 monthly]
 - Duration: weekly x 1-2 years
 - SF 2000µg/l = 84 weeks!
 - Monitor Hb, SF
- **Chelation** limited to cardiopathy
- **Diet** – Little benefit
- **Infections** – bugs need iron (*Vibrio* Sea foods, *Yersinia*)

