Heart Health – Understanding the function of iron

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Iron and Heart Health

- Understanding the role of iron in heart health is not just about understanding how iron (lack of or too much) affects heart function.
- In the field of heart failure we need to understand why iron is essential for normal health and how it contributes to co-morbidities often present in the HF population

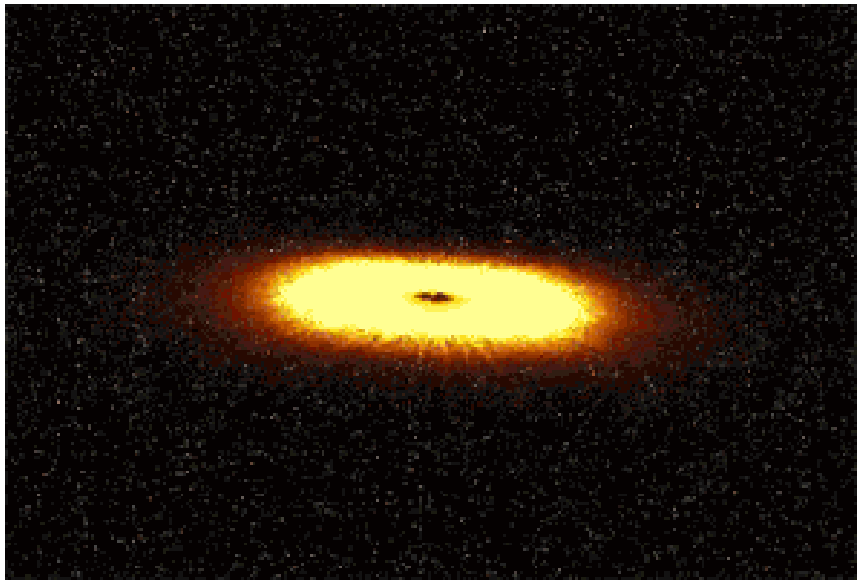
Objectives

- What is iron?
- Why do our bodies need iron?
- Sources and types of iron
- Overview of regulation and storage of iron
- Iron overload/deficiency
- Iron and the heart

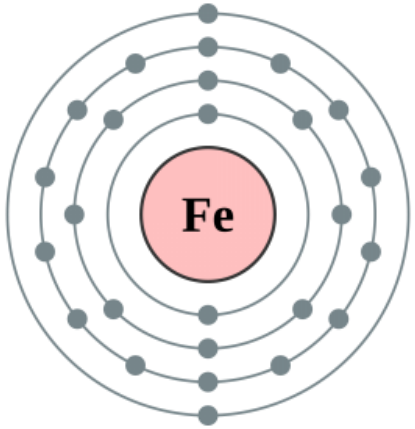
What is iron?

Most common element on Earth

Abundance is due to it being the last element to be produced with release of energy before the violent collapse of a supernova, which scatters the iron into space and across the universe



Essential element for almost all living organisms

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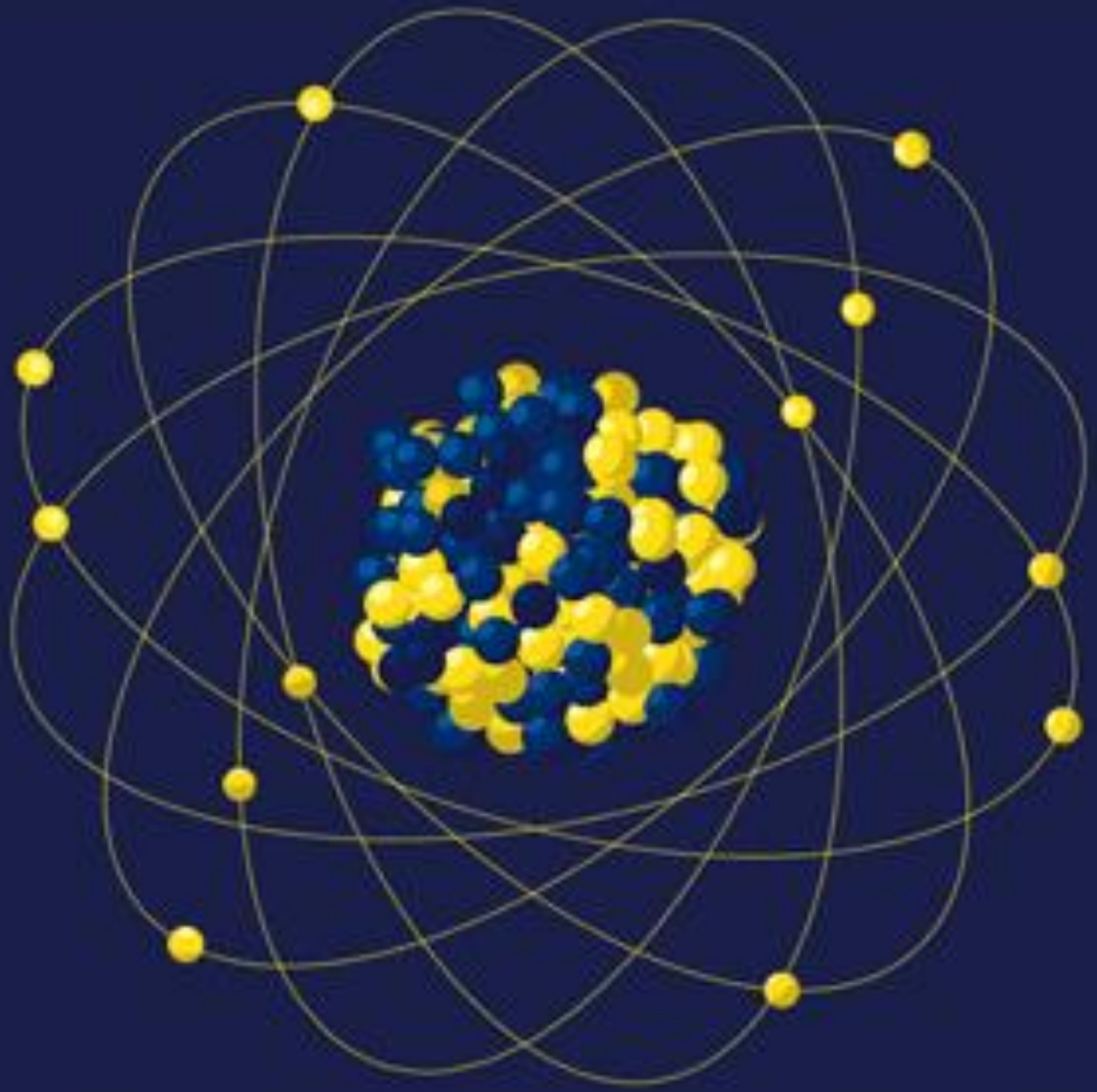


Atomic Structure – Electron Shells and Valence

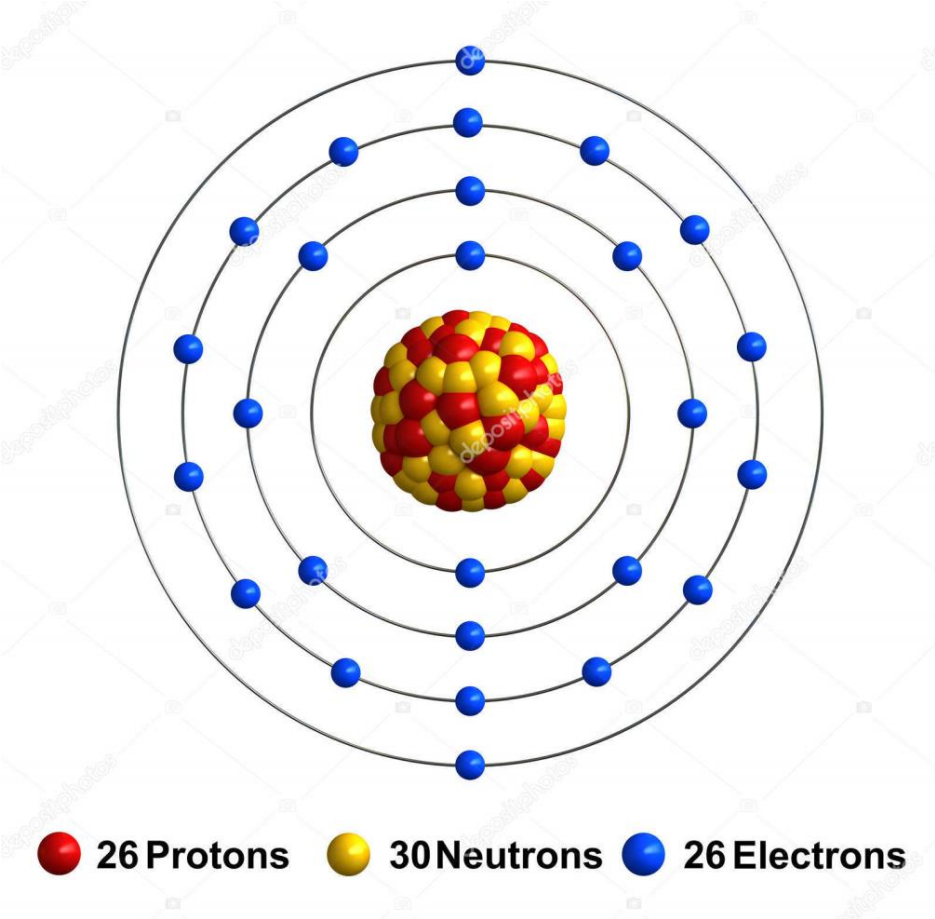
Shell	Subshell	Max electrons in subshell	Max electrons in shell
K	1s	2	2
L	2s	2	2 + 6 = 8
	2p	6	
M	3s	2	2 + 6 + 10 = 18
	3p	6	
	3d	10	
N	4s	2	2 + 6 + 10 + 14 = 32
	4p	6	
	4d	10	
	4f	14	

Atomic Structure of Iron

Shell	Subshell	Max electrons in subshell	Max electrons in shell
K	1s	2	2
L	2s	2	2 + 6 = 8
	2p	6	
M	3s	2	2 + 6 + 10 = 18
	3p	6	
	3d	6	
N	4s	2	2 + 6 + 10 + 14 = 32

Oxidation States of Iron

Oxidation state
–2 (d^{10})
–1 (d^{9})
0 (d^{8})
1 (d^{7})
2 (d^{6})
3 (d^{5})
4 (d^{4})
5 (d^{3})
6 (d^{2})
7 (d^{1})



Fe^{2+} Ferrous Iron

Fe^{3+} Ferric Iron (non-absorbable)

Why do our bodies need iron?

Why do our bodies need iron?

Oxygen transport and storage

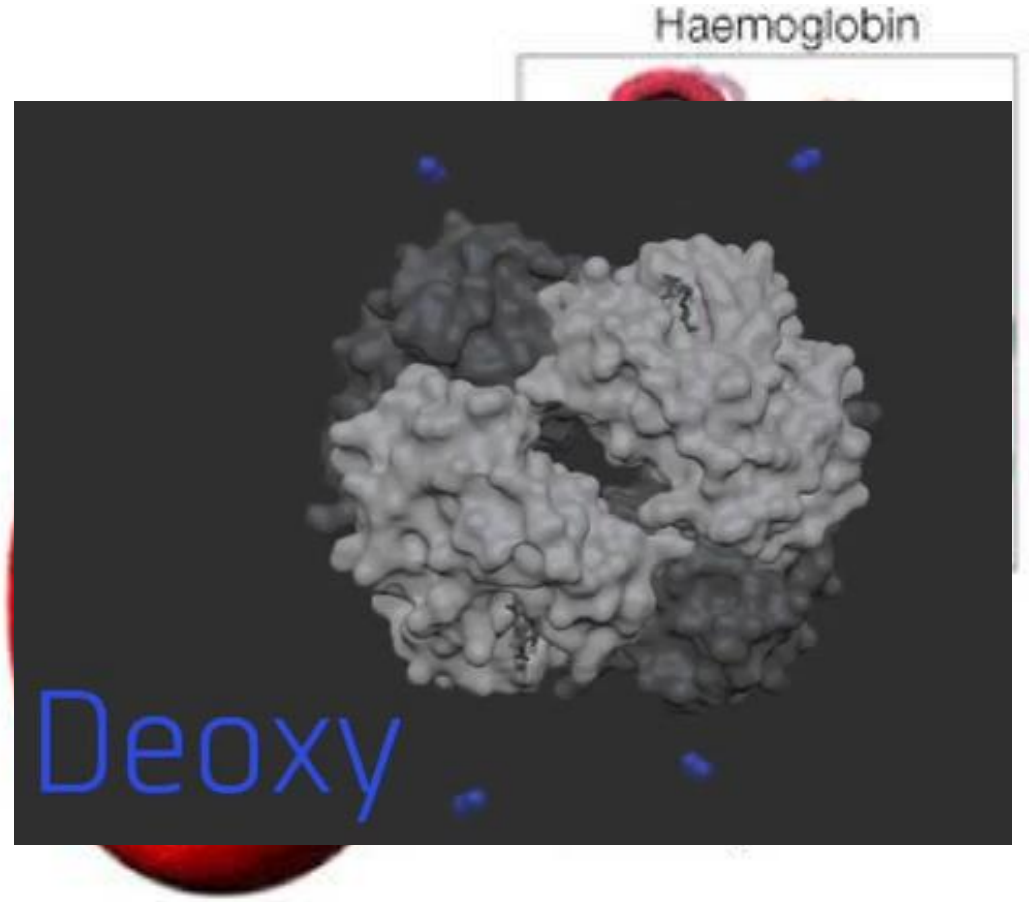
Oxygen Transport and Storage

Haemoglobin is the oxygen transport protein of the blood

'Normal' haemoglobin contains 4 protein subunits (2 alpha and 2 beta globin chains)

Each subunit has an associated iron (Fe2+) molecule (haem group)

Each iron molecule (i.e. subunit) can bind one oxygen molecule to form oxyhaemoglobin



Oxygen Transport and Storage

Myoglobin is the oxygen transport protein of the muscles

Only one haem group

Higher affinity for oxygen

Not usually found in blood stream – diagnostic testing

Haemoglobin

Why do our bodies need iron?

Oxygen transport and storage

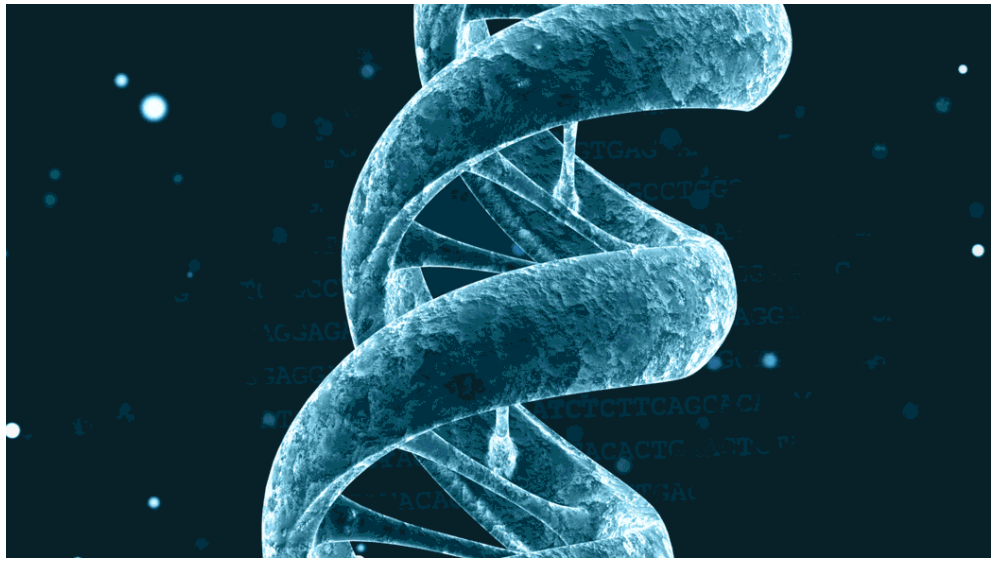
DNA , Enzymes and Cellular Energy

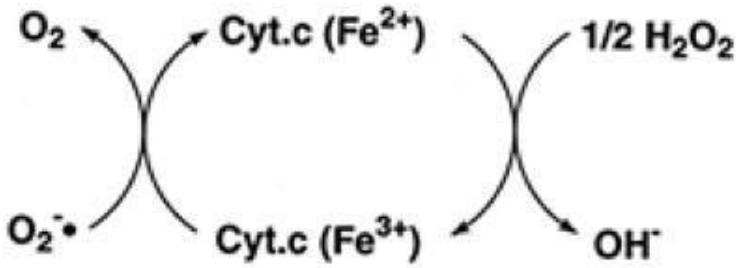
DNA, Enzymes and Cellular Energy

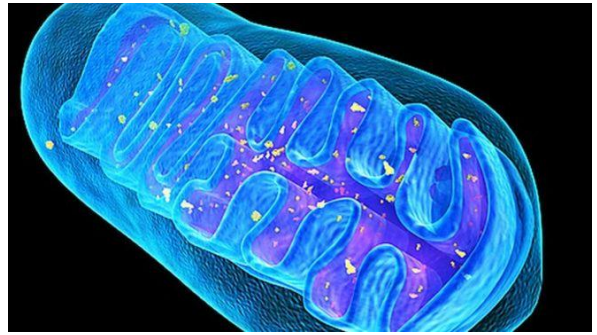
Numerous proteins involved in DNA replication and repair require iron as a cofactor

Cytochrome enzymes:

- Mitochondrial enzymes of electron transport chain (oxidative phosphorylation (Kreb's Cycle))
- hormone synthesis (including sex-hormones)
- cholesterol synthesis
- drug metabolism
- vitamin D metabolism
- apoptosis
- antioxidation



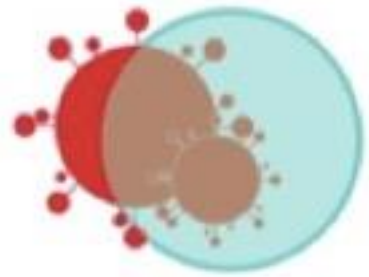




Why do our bodies need iron?

Oxygen transport and storage

DNA , Enzymes and Cellular Energy



Immunity

Immunity

Absolute requirement for iron by virtually all human pathogens

Regulation of iron distribution serves as an innate immune mechanism against invading pathogens

Innate immunity

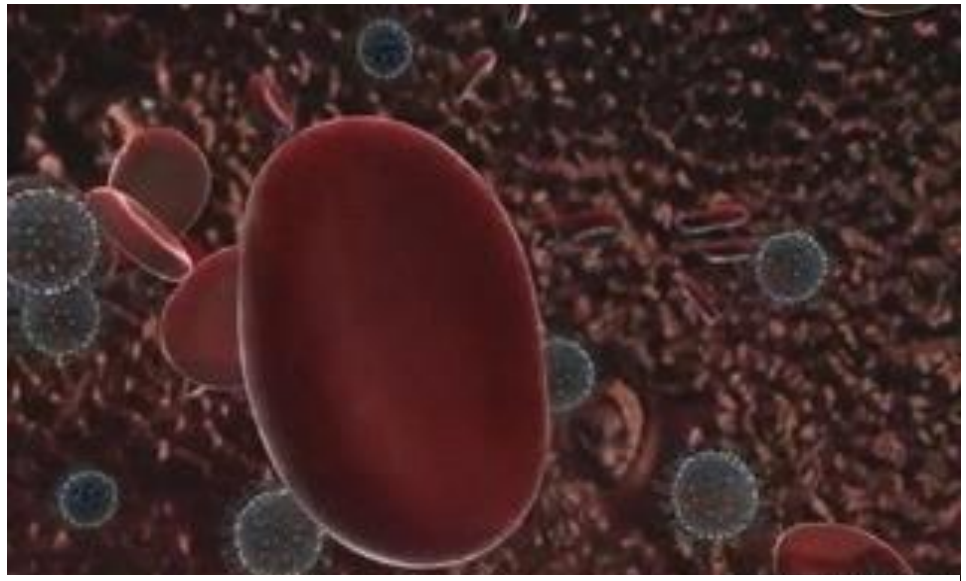
- Inflammatory cytokines and anti-microbial peptides by macrophages

‘Nutritional immunity’

- Majority of iron is intracellular
- Extracellular iron bound to proteins
- ‘Hypoferremic response’ to infection

Adaptive immunity

- Lymphocyte proliferation and function

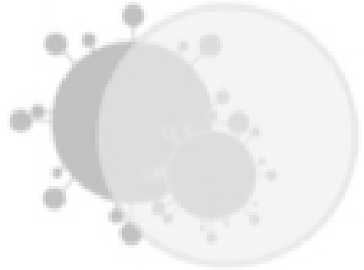


Why do our bodies need iron?

Oxygen transport and storage

Neurological Function

DNA , Enzymes and Cellular Energy



Immunity

Neurological function

Formation of myelin

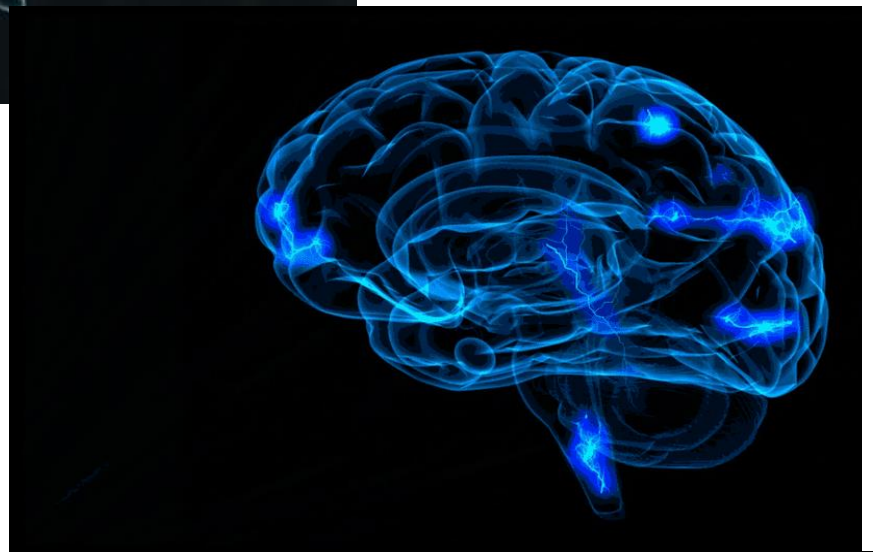
Development of neuronal dendritic tree

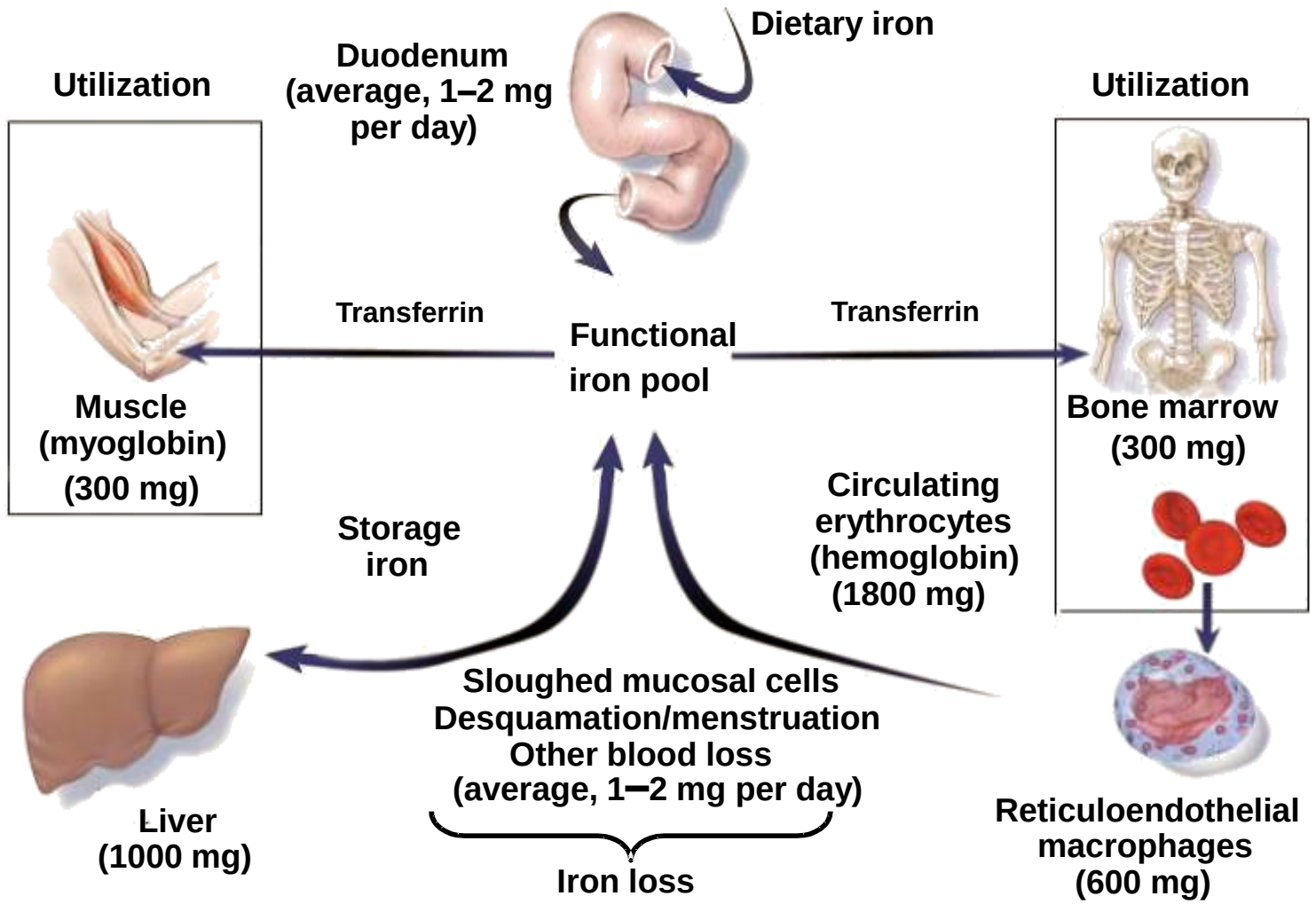
Neurotransmitters:

- dopamine
- adrenaline
- noradrenaline
- serotonin

Critical for normal brain function:

- learning, memory & mood





The human body has many mechanisms to absorb, transfer and store iron, but none to excrete it

Andrews NC. *N Engl J Med* 1999;341:1986–1995

Iron Sources

Iron represents approximately 35 and 45 mg/kg body weight in adult women and men, respectively

Not naturally produced

Humans rely on foods/supplements to meet daily requirements

90% of that consumed is conserved and re-used

There are two types of iron in food:

- Haem iron
- Non-haem iron

Haem Iron

- Haem iron is found only in animal foods
- Requires no chemical change for absorption
- Relatively unaffected by other factors
- Influenced to some extent by the body's iron stores
- The iron in meat is approximately 40% haem iron and 60% non-haem iron
- The average absorption of haem iron in meat is about 25%.

Non-haem Foods

- Non-haem iron is found in plant foods.
- It is not as well absorbed as haem iron (requires chemical change)
- Is affected by components in foods eaten at the same time.
- Is affected by the iron status of an individual
- Absorption of non-haem iron can vary:
  - Under 1% in an individual with replete stores
  - Up to 20% in an individual with depleted iron stores
- Generally non-haem iron absorption is less than 5%.

Regulation of cellular iron release

Dietary iron ingested in haem form directly absorbed via haem transporter

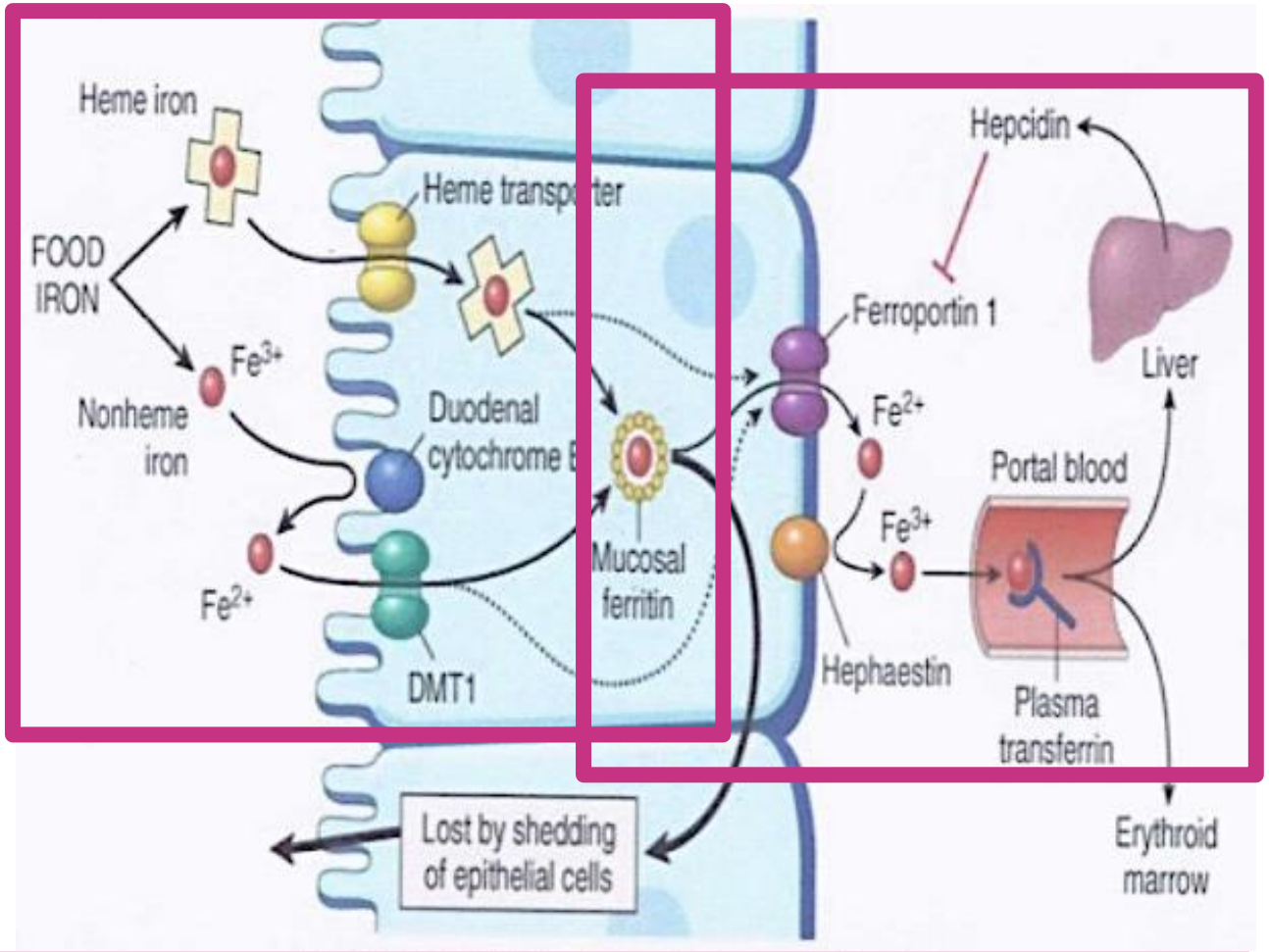
Ferroportin – transmembrane protein that releases ferrous iron from within the cells into the circulation

Dietary iron ingested in the non-haem (Ferric (Fe3+)) form is catabolisable

Hepcidin - regulatory hormone which down-regulates ferroportin and thereby prevents iron from entering the circulation

Fe3+ reduced to ferrous iron (Fe2+) which is absorbable

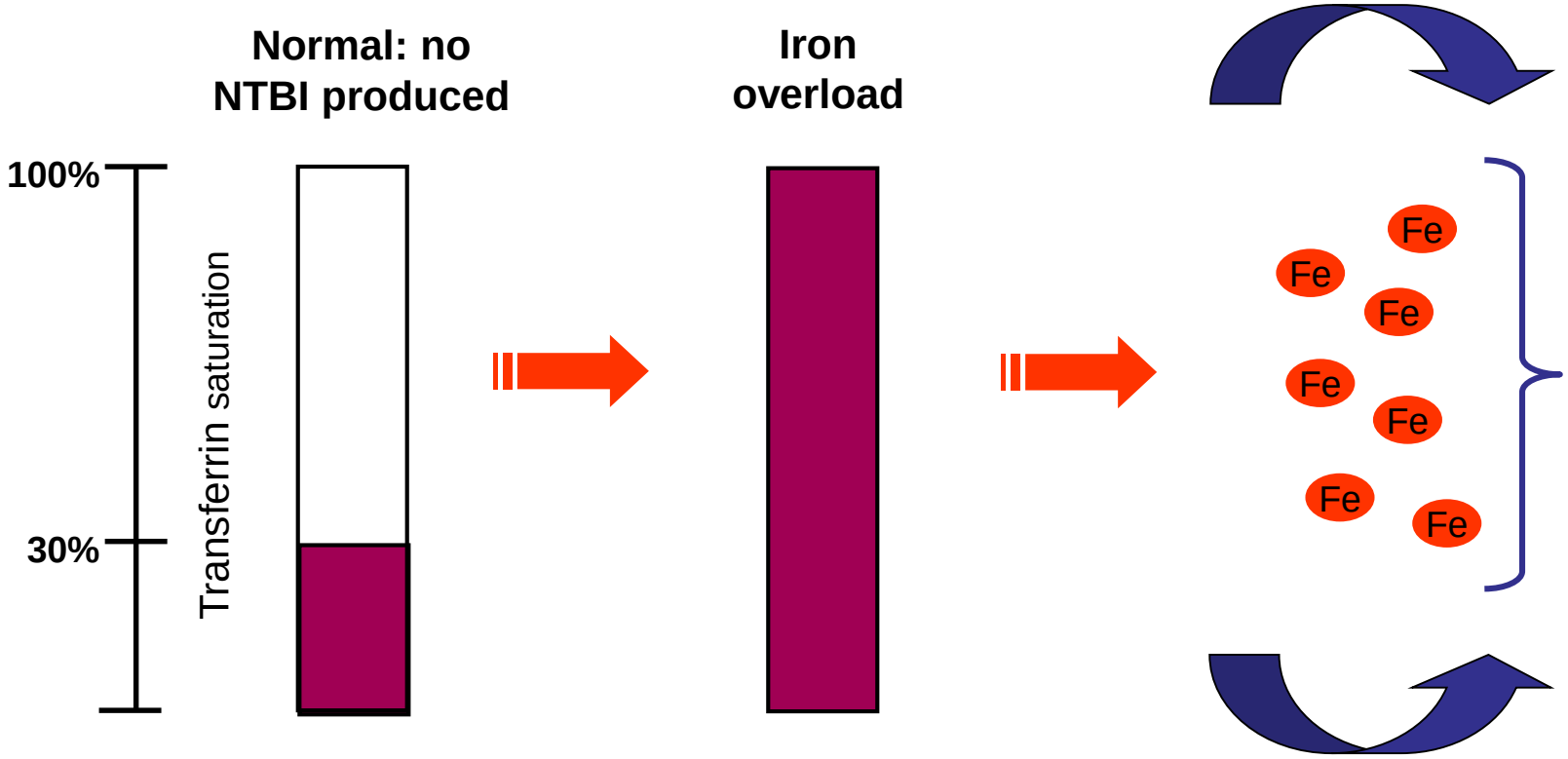
Ferric iron transported in blood bound to transferrin and stored in the liver as ferritin



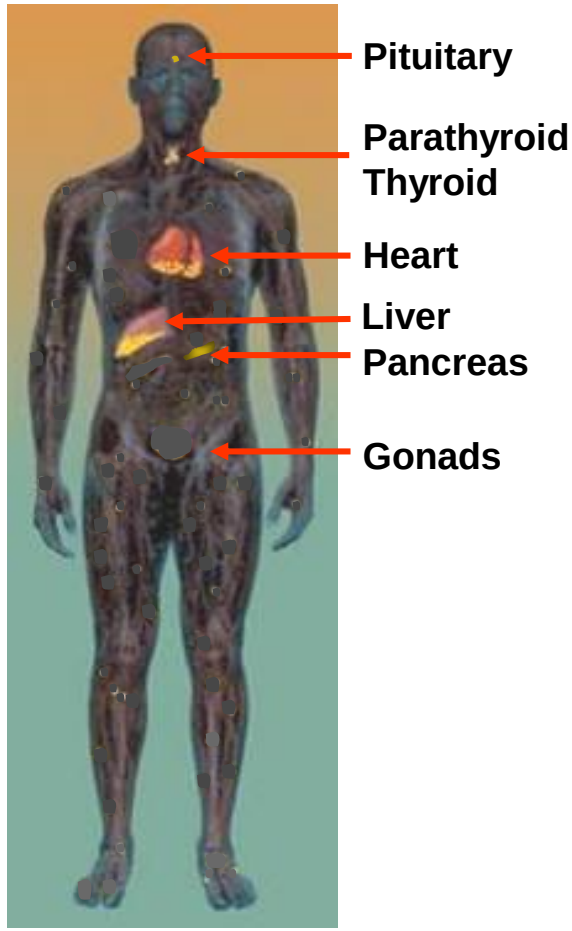
Iron Overload - formation of Non-Transferrin Bound Iron (NTBI)

Transferrin saturation due to:

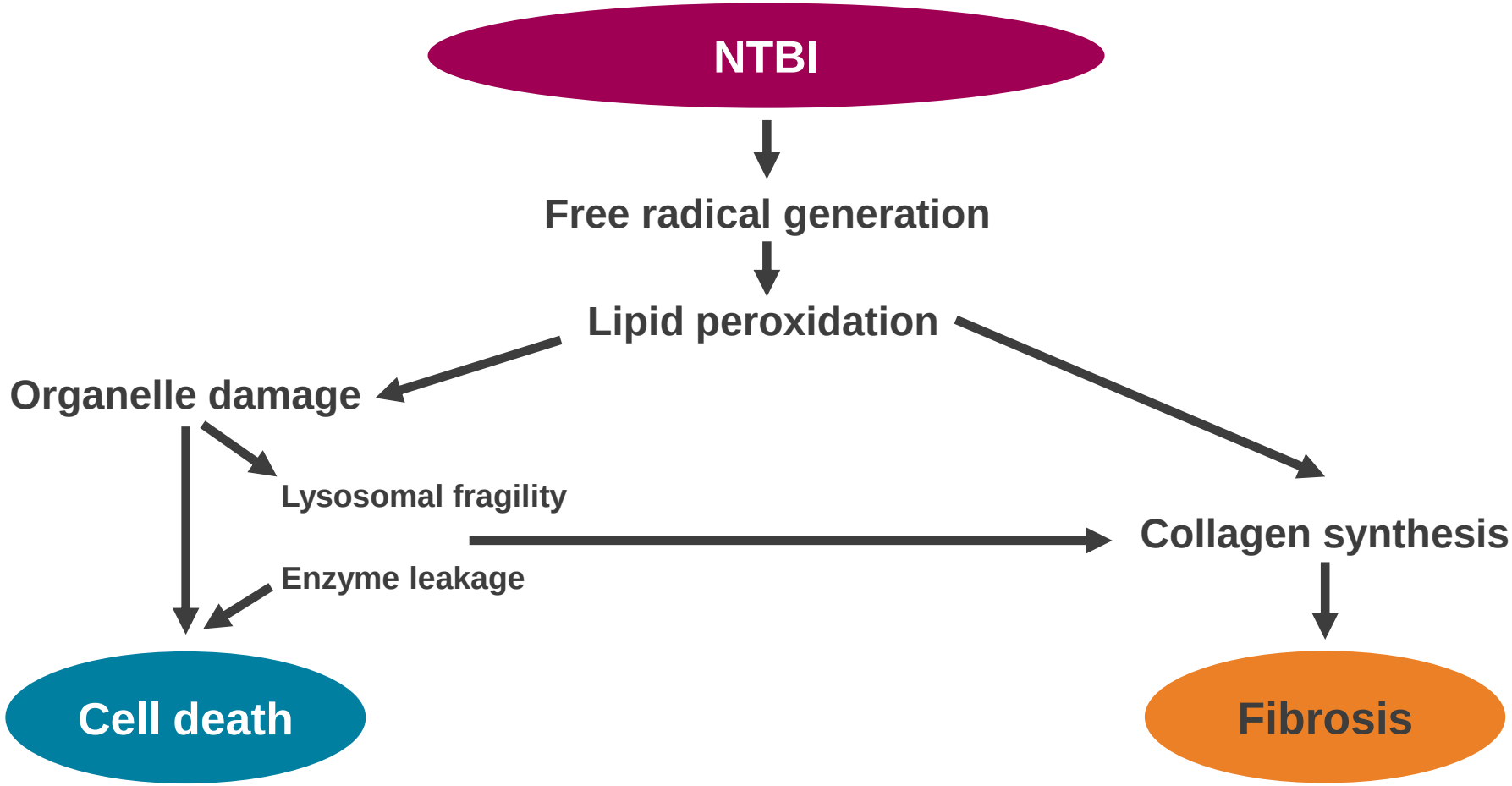
- **Frequent blood transfusions, or**
- **Ineffective erythropoiesis leading to increased iron absorption**



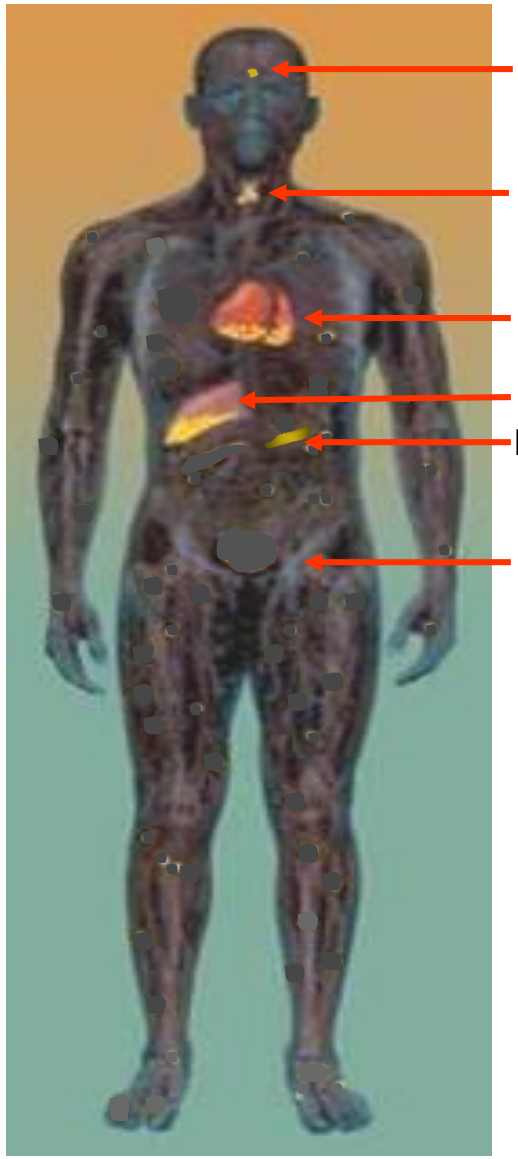
Uncontrolled iron loading of organs



Iron Overload – Cellular damage



Cohen AR and Porter JB. In Disorders of Hemoglobin: Genetics, Pathophysiology, and Clinical Management, Steinberg MH *et al.* (Eds); 2001:979–1027



- Endocrine disturbances → growth failure
- Cardiac failure
- Diabetes mellitus
- Liver cirrhosis/ fibrosis/cancer
- Infertility

Iron Deficiency – Cellular, Organ and Systemic Effects

Cellular

Mitochondrial dysfunction
Deranged activity of enzymes
Abnormal transport and structural proteins
Apoptosis

Organ

Tissue remodelling
Impaired organ efficiency

Systemic

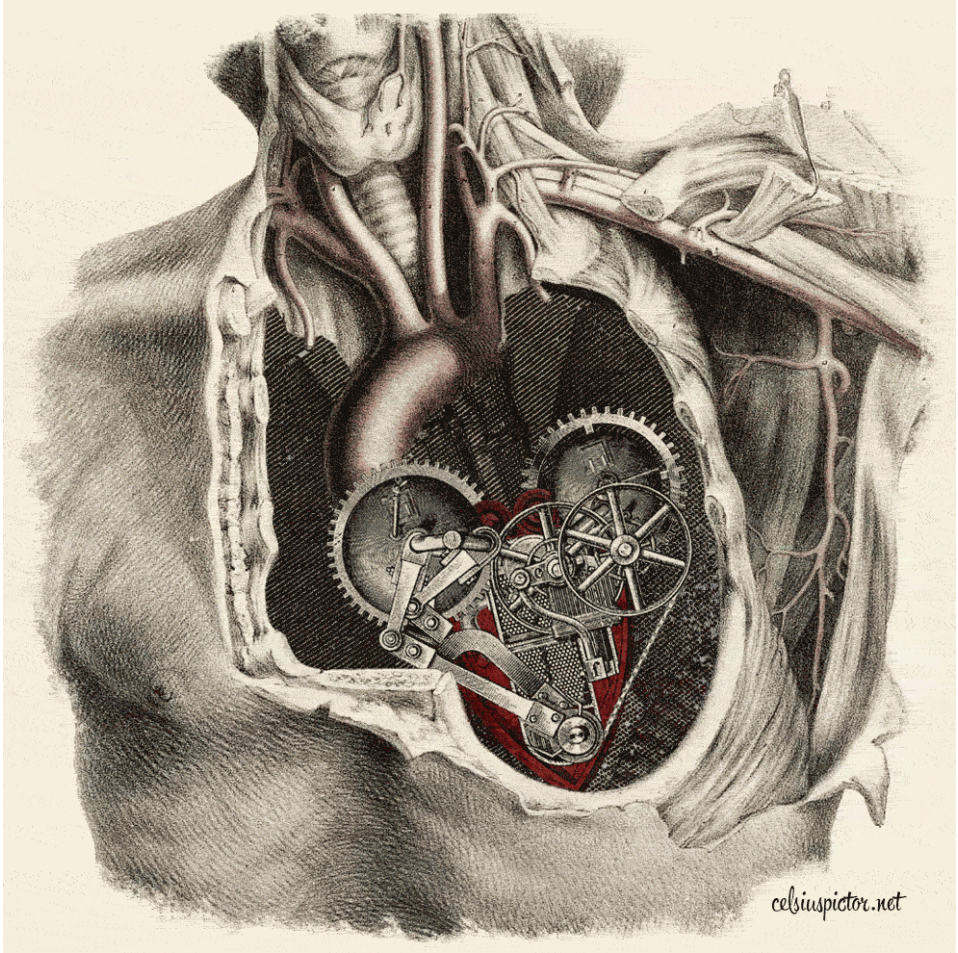
Impaired exercise capacity
Reduced work efficiency
Impaired cognitive performance and behaviour
Increased morbidity and mortality

Iron and the Heart

Detrimental effects on cardiac function in both iron deficiency and iron overload

Range of effects:

- Arrhythmias
- Diastolic dysfunction
- Systolic dysfunction
- Overt heart failure



Iron Deficiency and Heart Health

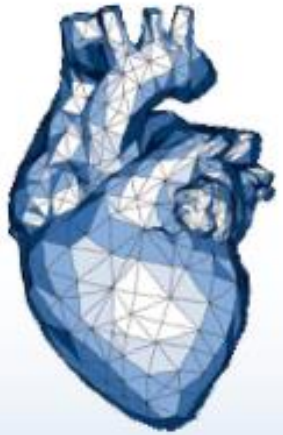
VIFOR PHARMA

2ND ANNUAL
NATIONAL HEART FAILURE NURSE MEETING

Heart Health
Improving patient outcomes in heart failure

Tuesday 25th September 2018

Radisson Blu, Manchester Airport



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Date of preparation: June 2018 UK/OTH/V18/0031b(1)

Agenda

09.00 Registration and refreshments

09.30 Chairs welcome and introductions
Dr John Baxter, Mrs Jayne Masters

09.40 Heart health – understanding the function of iron
Dr Sue Piper
Kings College Hospital NHS Trust

10.00 Iron deficiency and anaemia
Dr Ewan McKay
Countess of Chester NHS Trust

10.20 Consolidation and Q&A

10.40 Coffee

11.00 Interpretation of blood results - spot the difference?
Dr Parminder Chaggar
Sheffield NHS Trust

11.20 Clinical data update and options for iron replacement
Dr Simon Williams
UHSM NHS Trust

11.40 Consolidation and Q&A

12.00 Coding in Heart Failure
Dr Sue Piper
Kings College Hospital NHS Trust

12.10 Lunch

13.10 Introductions from afternoon chairs
Dr Simon Williams, Mrs Annie MacCallum

13.20 Implementation of guidelines
Dr Carla Plymen
Imperial College Healthcare NHS Trust

13.50 Consolidation and discussion

14.20 Interactive patient case study session
Dr Carla Plymen
Imperial College Healthcare NHS Trust

14.50 Coffee

15.10 Iron deficiency and frailty - holistic patient care
Dr Robin Ray
St George's NHS Trust

15.30 The importance of activity in heart failure
Louise Clayton
University Hospitals of Leicester

16.00 Interactive patient case study session
Dr John Baxter
Sunderland NHS Trust

16.20 Summary & Close

Vifor Pharma UK have fully funded this meeting, including the honoraria for the chair and speaker and have contributed to the design of the agenda. The case studies, slides and clinical content are the speaker's own.

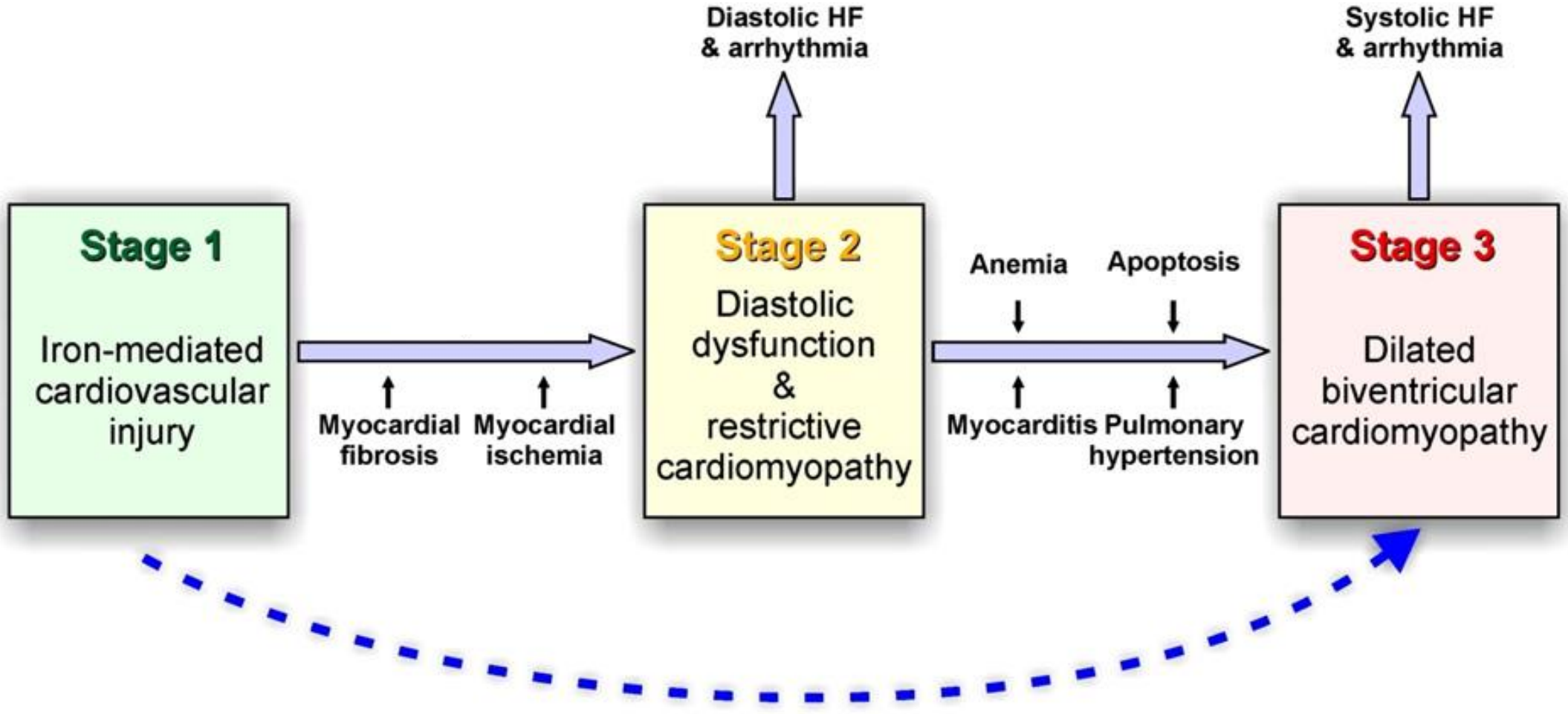
Iron Overload and Heart Health

Inherited iron overload syndromes
HFE related hemochromatosis (Type 1)
C282Y/C282Y
C282Y/H63D
Other *HFE* mutations
Non-*HFE* related hemochromatosis
Juvenile Hemochromatosis (Type 2)
Type 2A – Hemojuvelin mutations
Type 2B – Hepcidin mutations
Transferrin receptor 2 hemochromatosis (Type 3)
Ferroportin diseases (Type 4)
Classical
Nonclassical

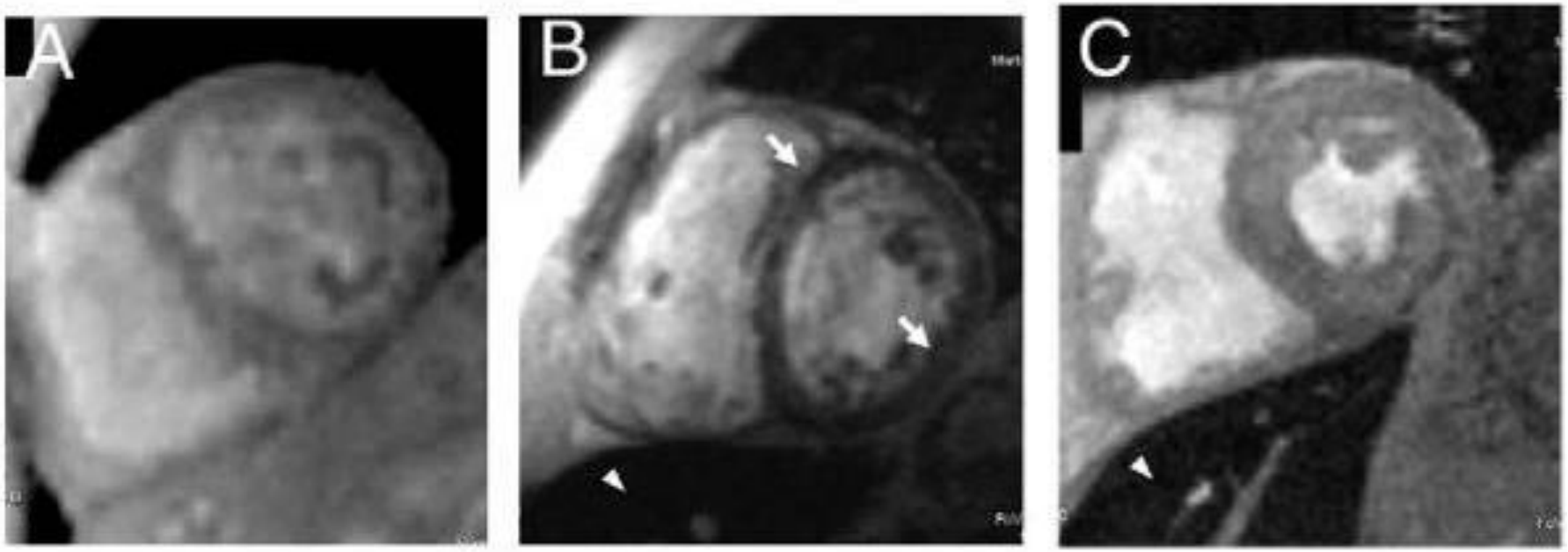
Secondary iron overload syndromes
Iron-loading anaemias
Thalassemic syndromes (β Thalassaemia)
Sideroblastic Anaemias
Chronic Hemolytic Anaemia
Aplastic Anaemia
Pyruvate Kinase Deficiency
Chronic liver disease
Hepatitis C infection
NAFLD
Alcoholic liver disease
Porphyria Cutanea Tarda
Iatrogenic
Red Blood cell transfusion
Long-term hemodialysis
Miscellaneous
Aceruloplasminaemia
African iron overload
Neonatal iron overload

Siddique, A. & Kowdley, K.V. Aliment Pharmacol Ther 2012; 35: 876–893

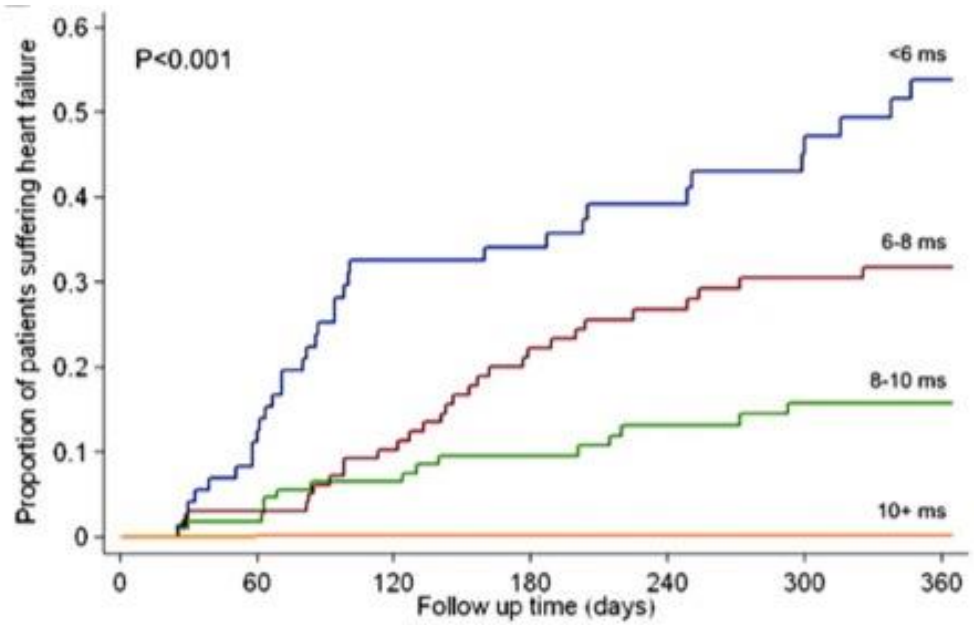
Iron Overload Cardiomyopathy – Cardiac Dysfunction

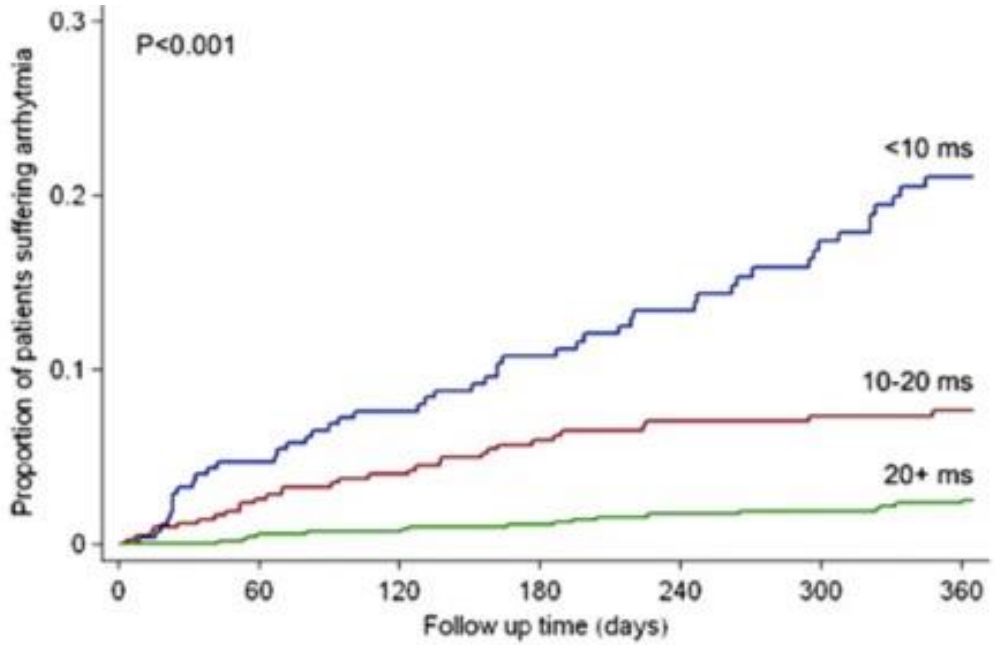


Iron Overload Cardiomyopathy – CMR T2*

	45 year old male with idiopathic CM	35 year old female with sickle cell anemia	45 year old male with HH
			
Iron Overload	Heart (-) Liver (-)	Heart (+) Liver (+)	Heart (-) Liver (+)

Iron Overload Cardiomyopathy – Prognosis





Conclusions

- Iron is an essential element for normal human health
- Ability to accept and donate electrons underpins its role in both normal and abnormal physiology
- Human body relies on external sources of iron
- Requires tight regulation
- Abnormalities in its processing and abundance have direct effects on heart health
- Significant role in other physiological functions that contribute to the heart failure syndrome