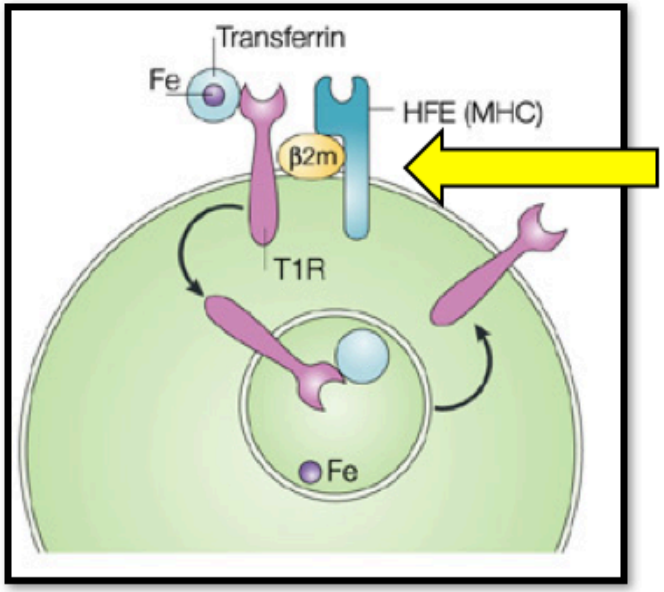
Podcast (Video Recorded Lecture Series):
Metabolic Liver Diseaeses (Part I), Hemochromatosis for the USMLE Step One Exam



Howard J. Sachs, MD
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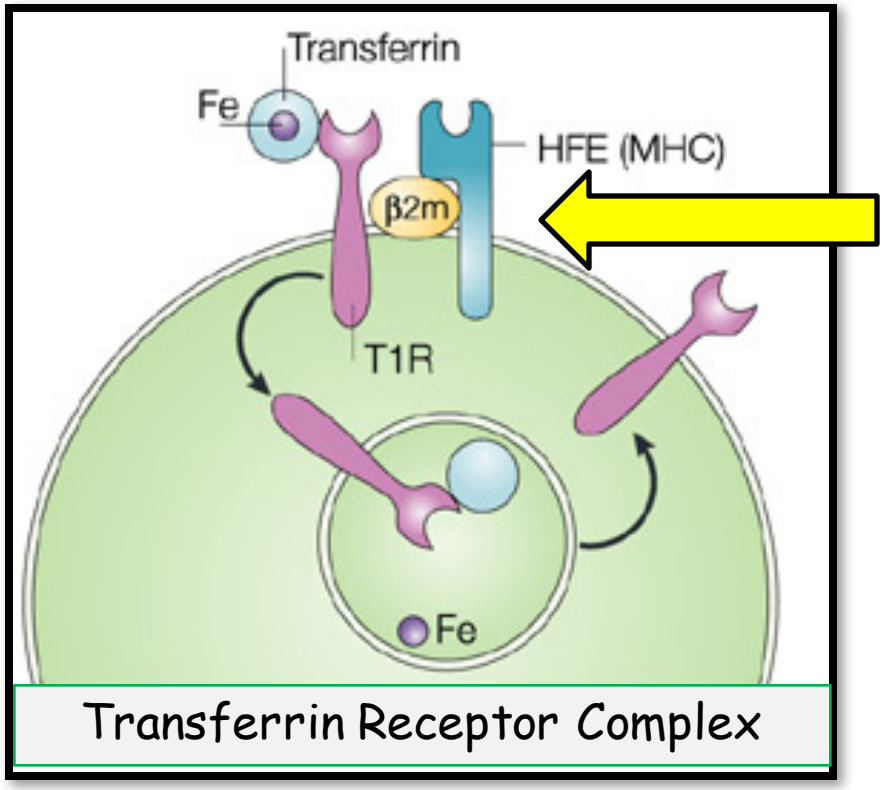
Metabolic Liver Diseases (for the Boards)

HH	Iron dysregulation (understand the factors involved) Multisystem (which systems?) Diagnostic Lab Studies and key stains? Complications
Wilson's	Copper dysregulation (understand the mechanisms involved) Multisystem (which systems?) Diagnostic Lab Studies and key stains? Complications
α-1-antitrypsin	Protein dysregulation Diagnostic Lab, Biopsy Findings and key stains.

Metabolic Liver Diseases (for the Boards)

HH

Iron dysregulation (understand the factors involved)
Multisystem (which systems?)
Diagnostic Lab Studies and key stains?
Complications



Transferrin Receptor Complex

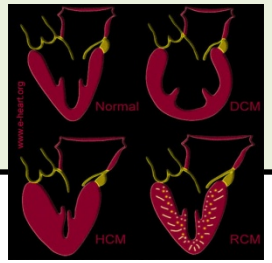
Metabolic Liver Disorders,

(Hereditary) Hemochromatosis: A Sensing Defect

Iron Overload: Can't stop absorbing the damn stuff

How do these patients present?

1. Iron sets off sensors at airport scanners
2. They get sucked into MRI machines?
3. They rust?
4. Other?...can you name the 6 organs?



Metabolic Liver Disorders,
(Hereditary) Hemochromatosis: A Sensing Defect

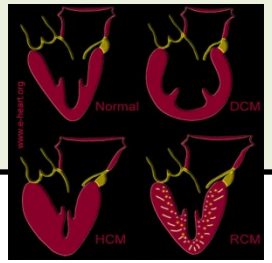
Iron Overload: Can't stop absorbing the damn stuff

- MM, heart, kidney
- Patterns:
  - 2:1 alcohol
  - Elevations into 1000's: shock, toxins, viral hep
  - Degree of elevation ≠ gravity of cause

What pattern of enzyme elevation would you expect in hemochromatosis?

Can this disease cause cirrhosis or HCC?




To do hemochromatosis, you have to do iron…

Rule One: Can only regulate iron absorption, not excretion

So who are the players?

Absorption:

Carrier/Storage:

Regulators:

To do hemochromatosis, you have to do iron…

Rule One: Can only regulate iron absorption, not excretion

So who are the players?

Absorption:
Enterocyte ('duodenocyte')
DMT
Ferroportin (basolateral surface)

Carrier/Storage:
Transferrin
Ferritin

Regulators:
Tfr/HFE (regulates absorption)
Hepcidin (regulates movement)

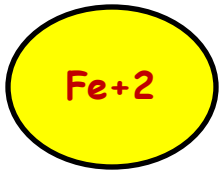
Best way to think about HH is to understand iron metabolism and iron deficiency anemia.

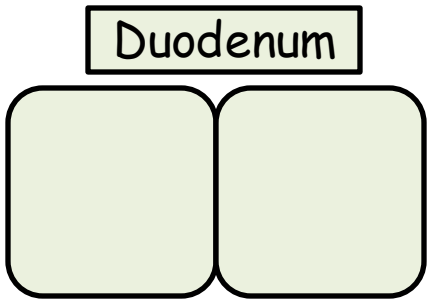
HH physiology is the body acting like it has IDA (forever).

So, how is iron absorption regulated?

FYI…
You need iron for other sections
so I've beaten it to death

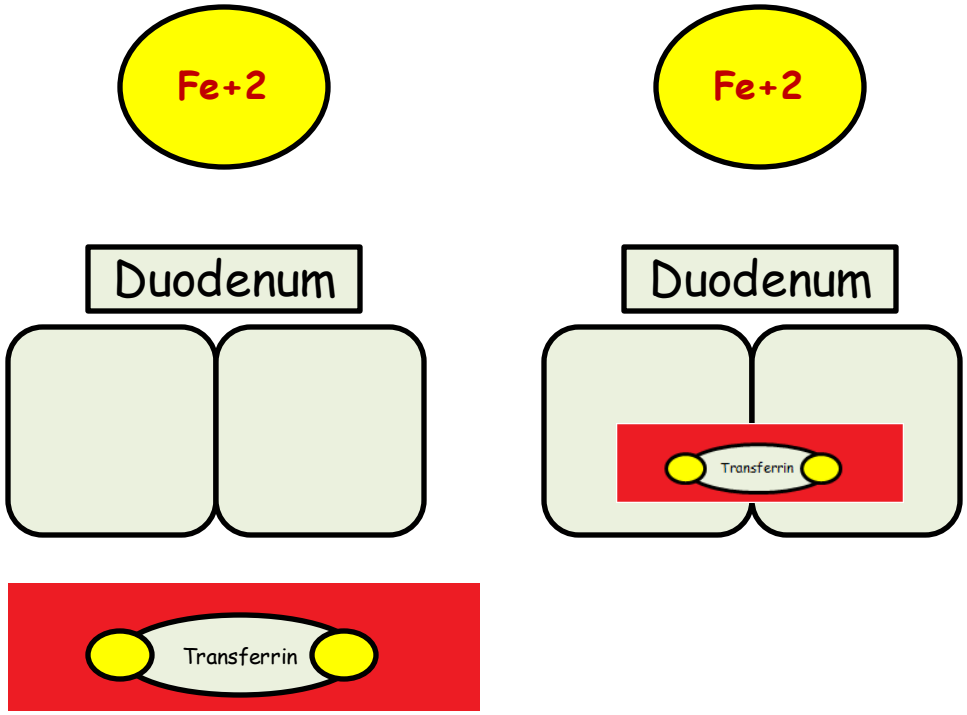
To absorb or not to absorb, that is the question?





To absorb or not to absorb, that is the question?

If lots of transferrin in the duodenocyte, iron won't be absorbed.



Iron is transported attached to Transferrin

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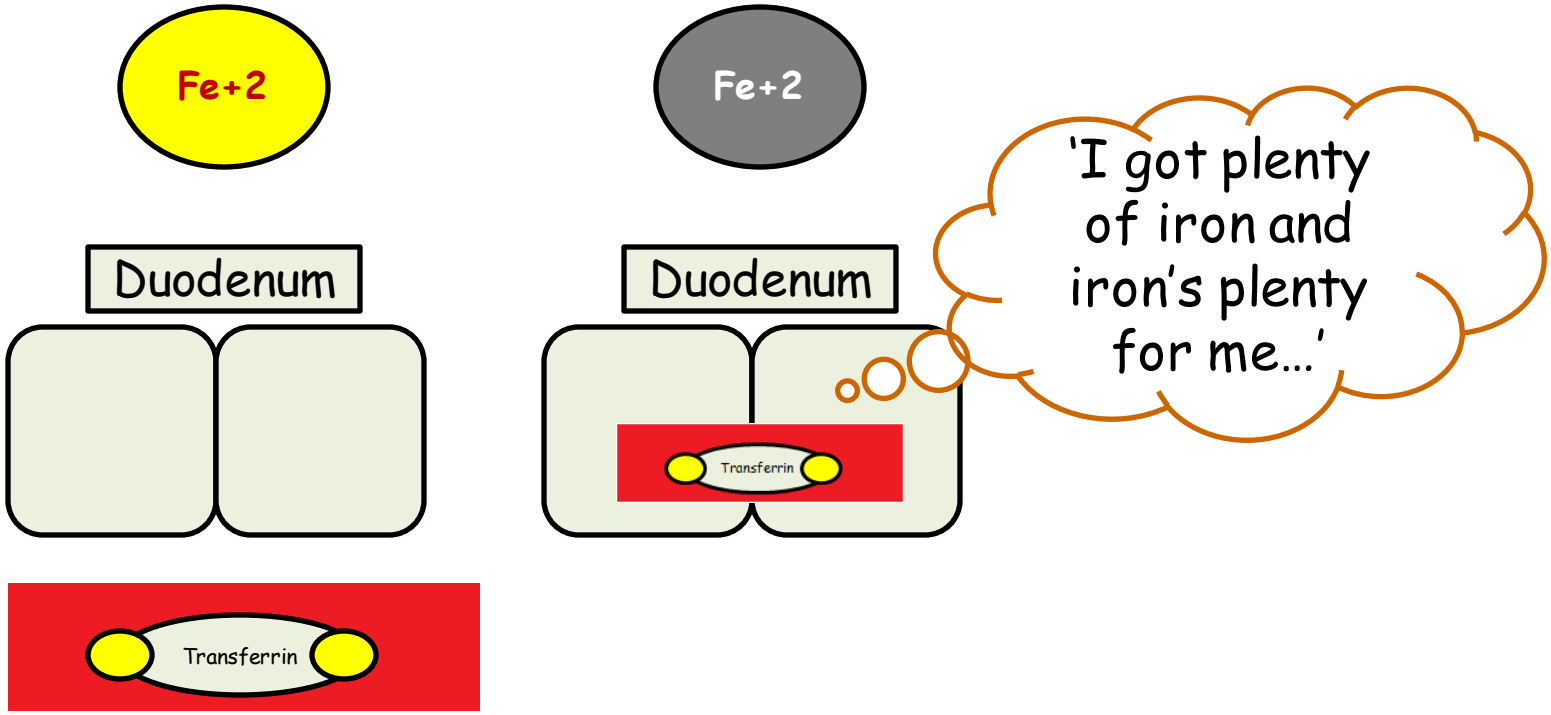

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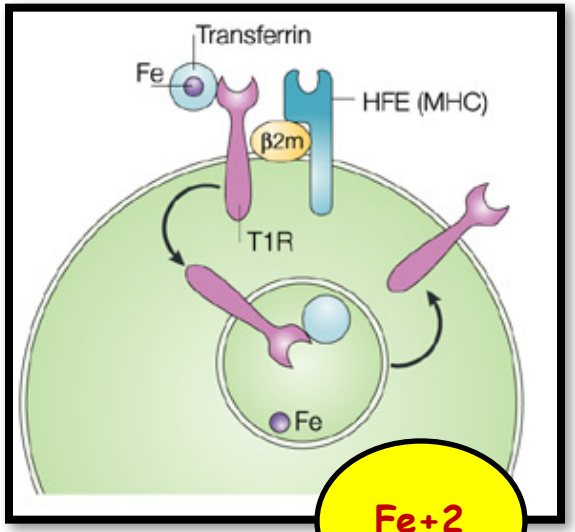


Fe+2

Duodenum

Transferrin

Fe+2

Duodenum

Transferrin

HFE

β-2 MG

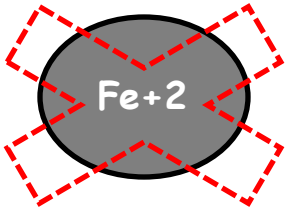
Tfr

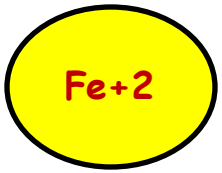
Transferrin

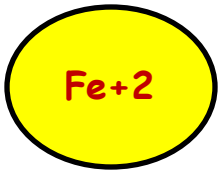
How did that Transferrin-Iron complex get in there?

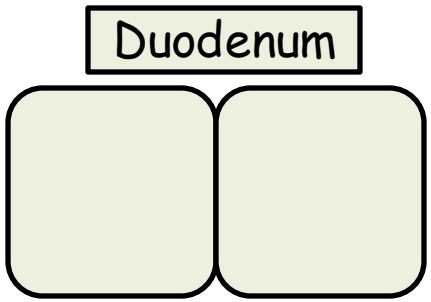
To absorb or not to absorb, that is the question?

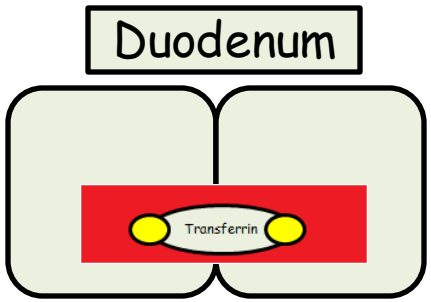
If lots of iron in the duodenocyte, iron won't be absorbed.

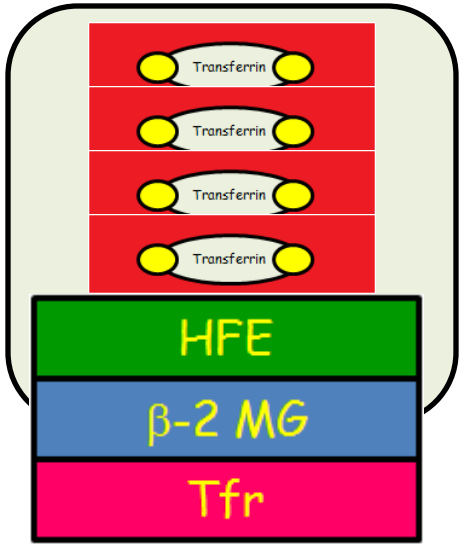










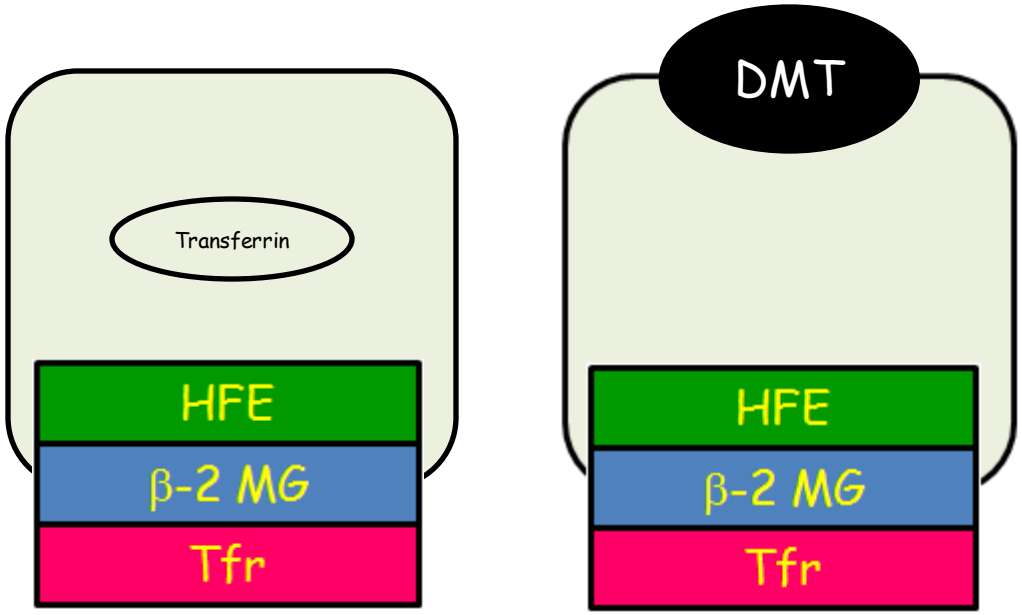


Body regulates absorption
It makes that decision based on how much iron is contained in the enterocyte

That decision, in turn, is dependent on a normally functioning Transferrin Receptor Complex

But, if hungry for iron, what happens next?

Upregulation of DMT in crypt



Duodenal Crypt

But, if hungry for iron, what happens next?

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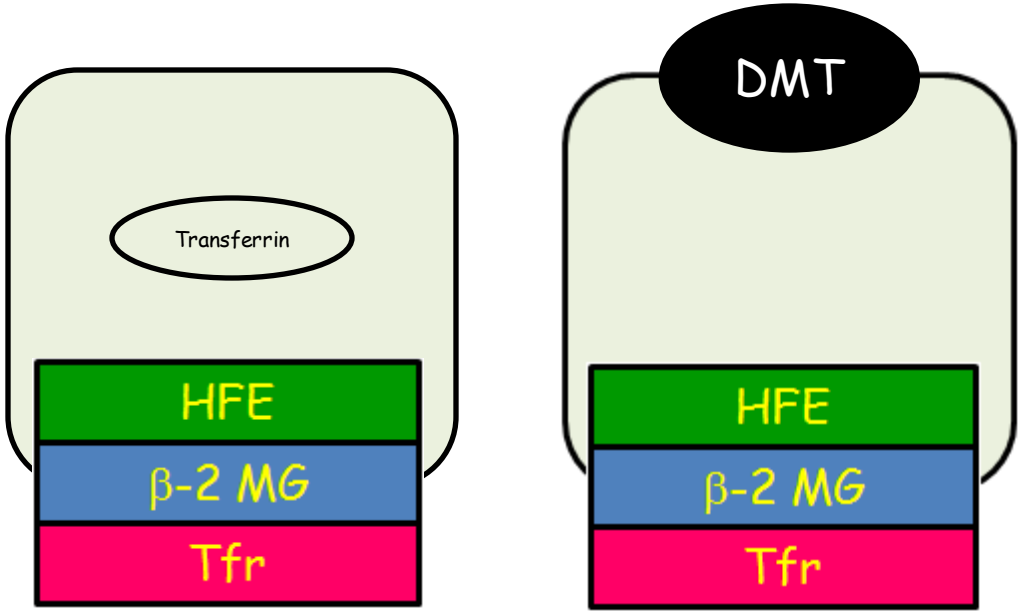
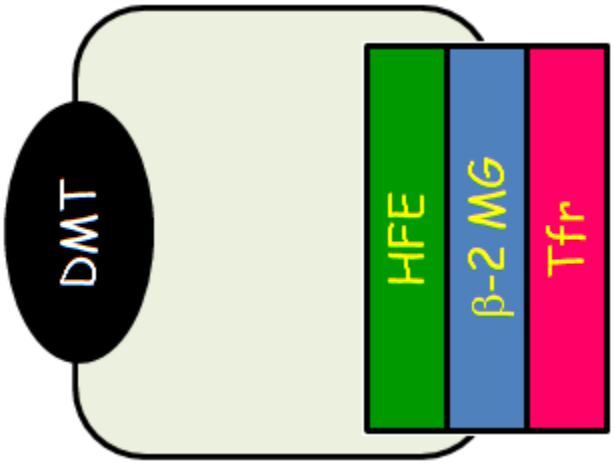
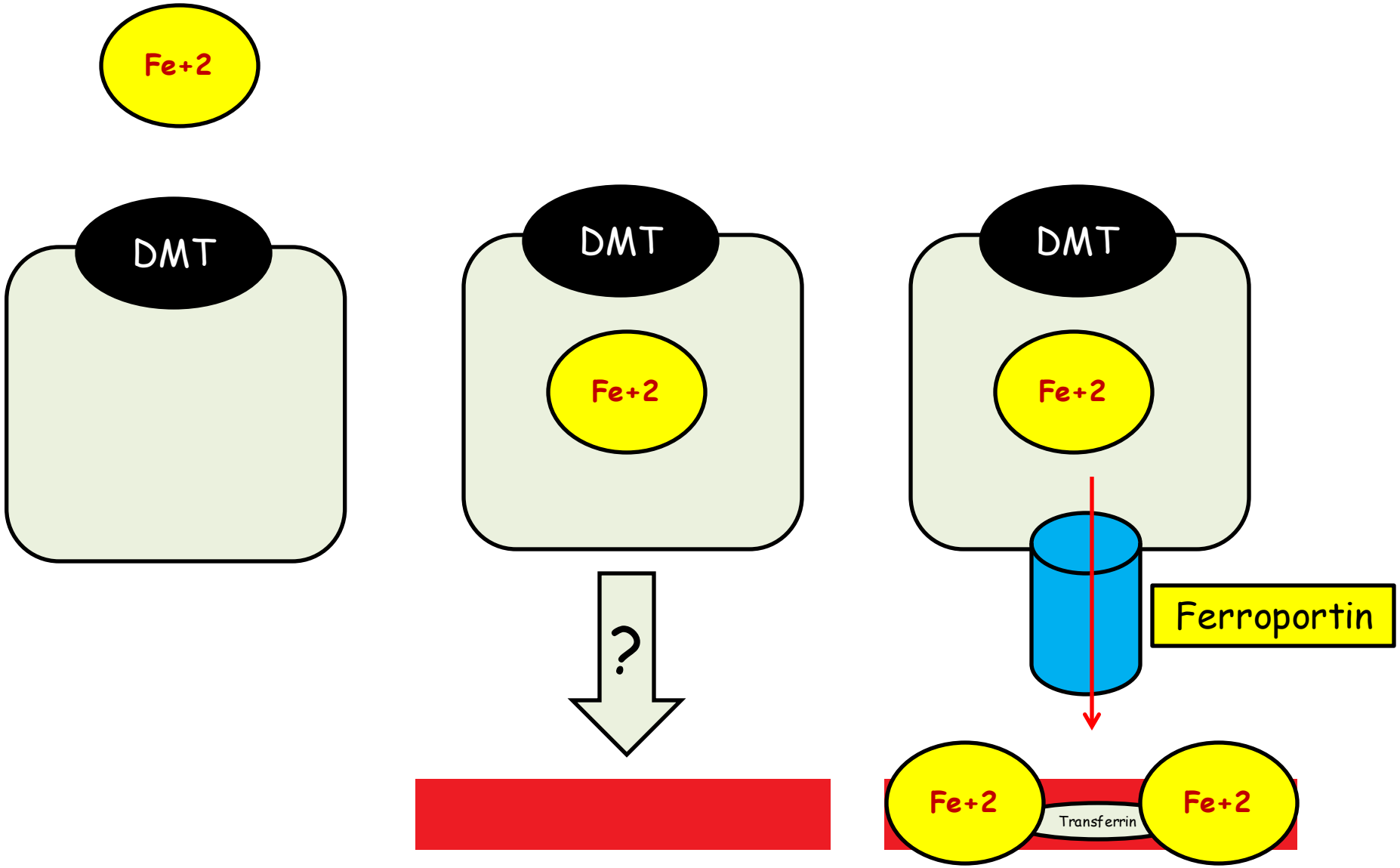
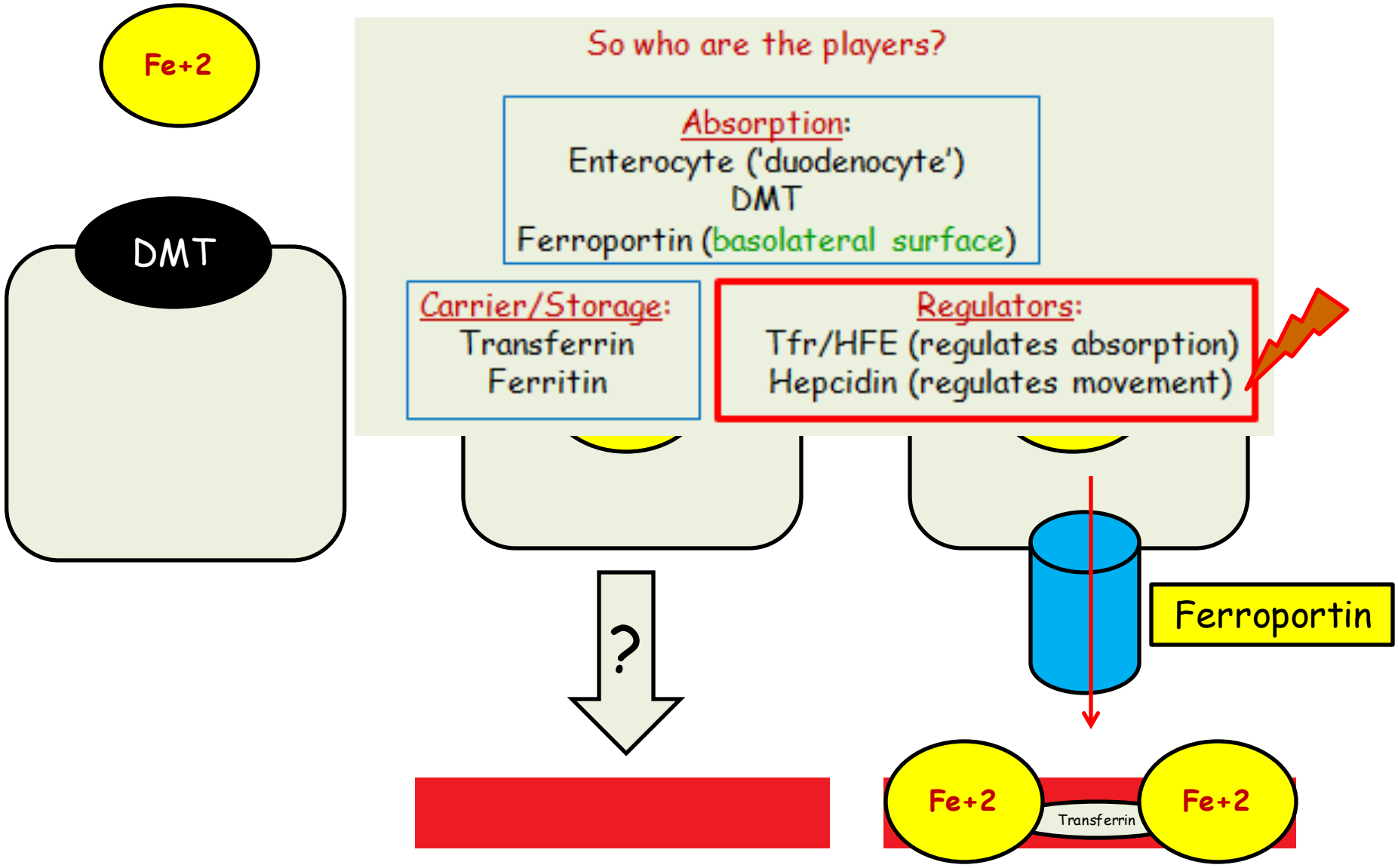




Upregulated crypt cell migrates to villous

Duodenal Crypt


Fe+2
DMT
DMT
Fe+2
?
DMT
Fe+2
Ferroportin
Fe+2
Transferrin
Fe+2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Fe+2
Transferrin
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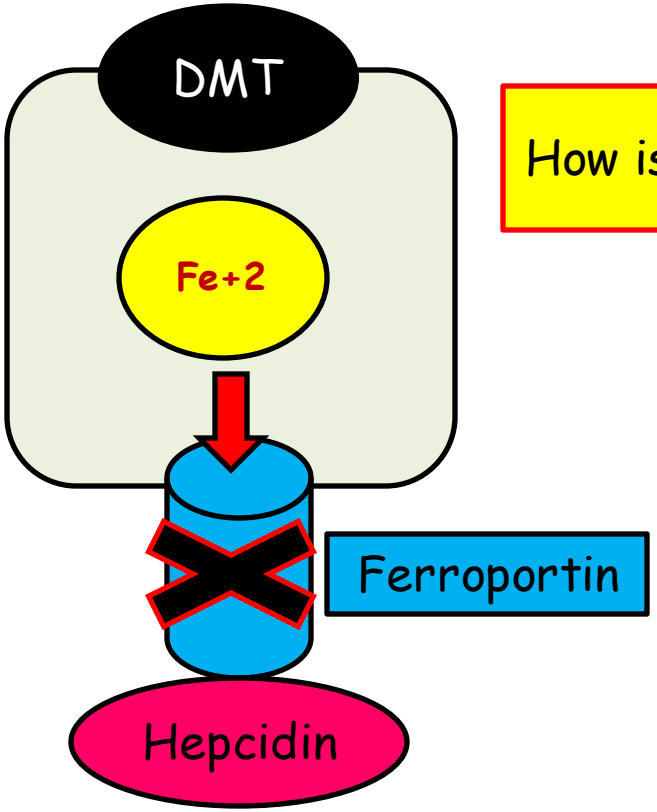
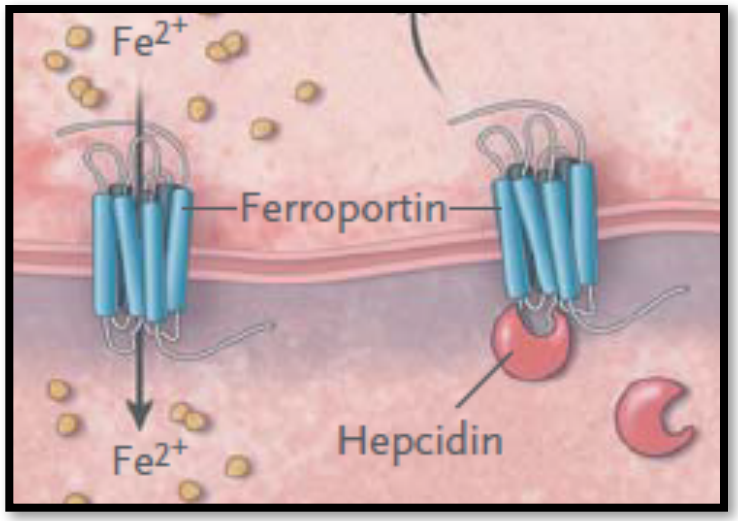


How is iron movement regulated?

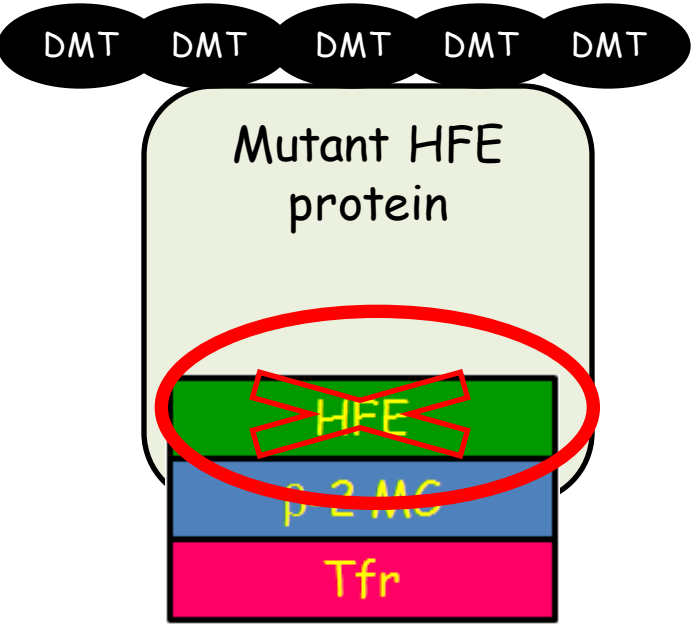


Hepcidin is a protein made in liver.
It regulates MOVEMENT of iron.
With iron deficiency, hepcidin level is low and there is free movement of iron.
With adequate iron, hepcidin degrades ferroportin effectively trapping iron in cells.

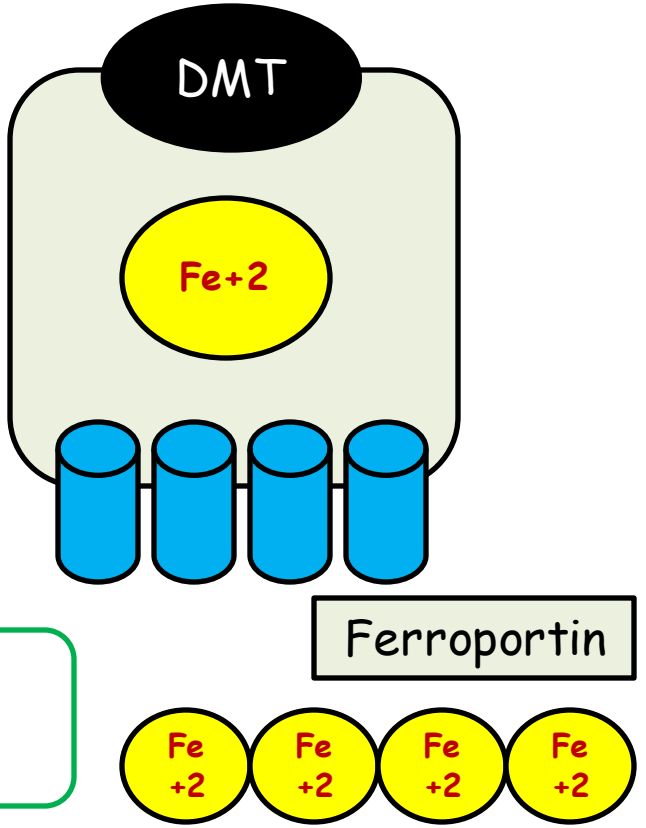
What are the (2) defects in hemochromatosis:

1. Enterocyte doesn't sense iron as a result of a defective Tfr/HFE complex (so upregulates DMT and thereby absorption).

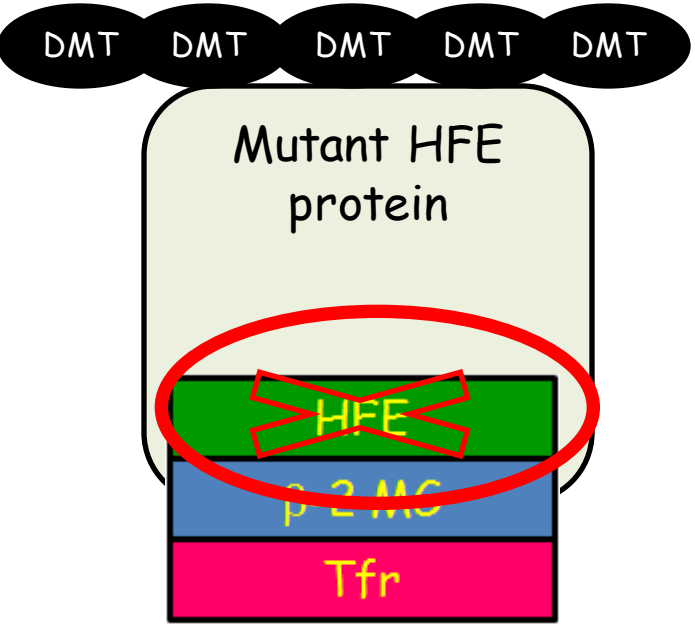
2. Hepatocyte doesn't sense iron so downregulates Hepcidin and iron is free to move throughout the body and specifically through the ferroportin channel (basolateral surface).



↓↓ Hepcidin:
Come right in!



This was a long crazy tale but I have seen questions on every aspect of iron metabolism and the relationship to HH.



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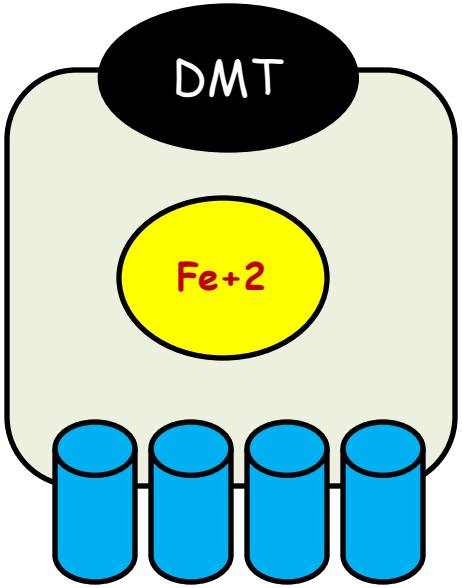
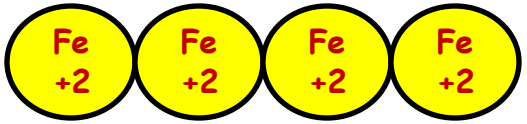
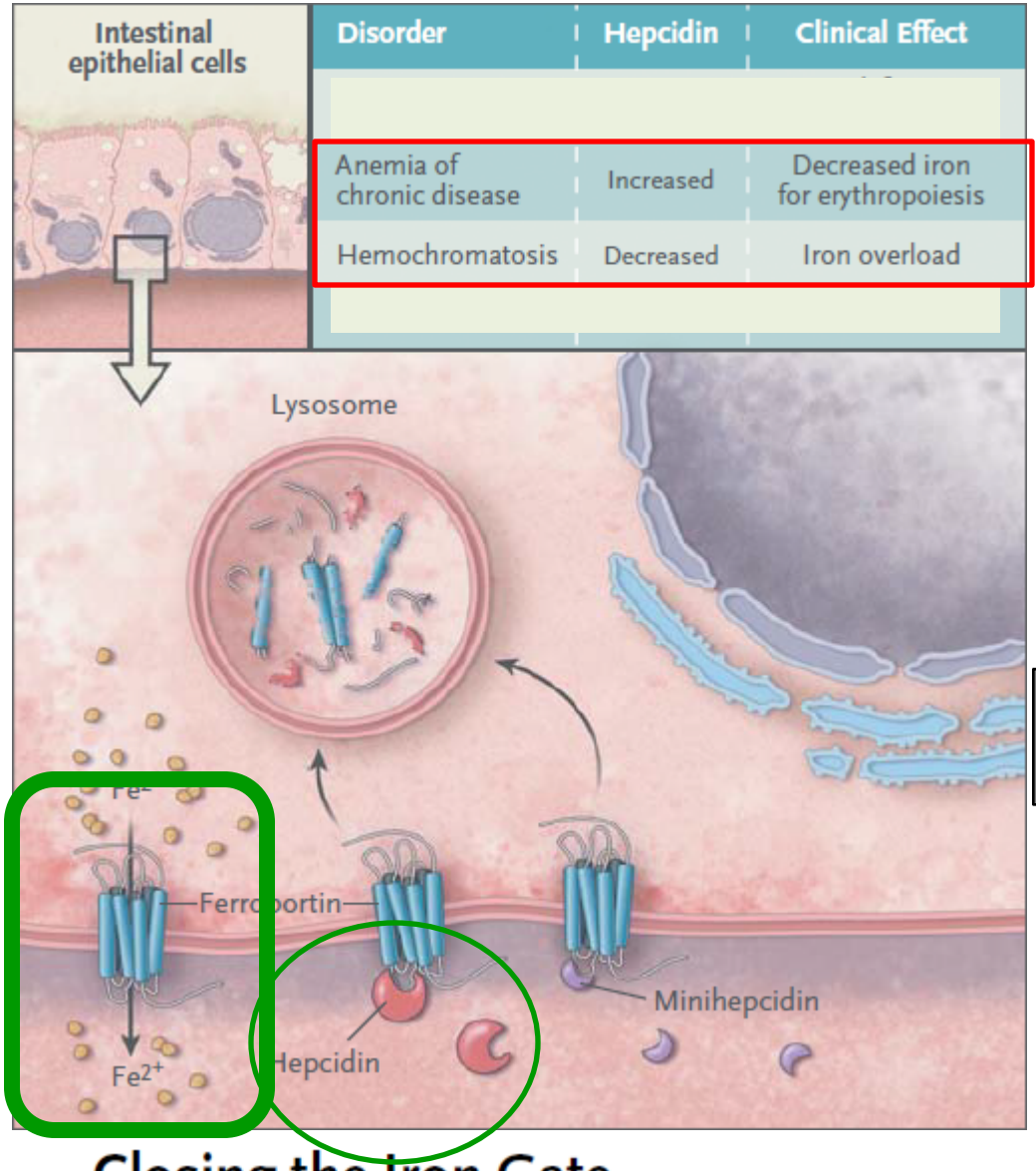


Ferroportin





Closing the Iron Gate

Nancy C. Andrews, M.D., Ph.D.

N ENGL J MED 366;4 NEJM.ORG JANUARY 26, 2012

ACD: IL-1 stimulates Hepcidin and iron is trapped (in RES). EPO is also inhibited

Hepcidin infusion can technically be used to rx HH

Hepcidin: The On-Off Switch of Iron Movement

Metabolic Liver Disorders, (Hereditary) Hemochromatosis: A Sensing Defect

Iron Overload: Can't stop absorbing the damn stuff

- Background/Presentation:
  - AR disorder of intestinal iron absorption
    - Cannot regulate iron excretion, only absorption
  - Excess iron deposits damages multiple organs: liver, heart (CHF), skin/pancreas (Bronze Diabetes), joints (OA/CPPD), pituitary/hypothalamus (ED).

National Board of Medical Examiners

Subject Examination Program

Examinee Performance Profile

Comprehensive Basic Science

Multisystem Processes & Disorders

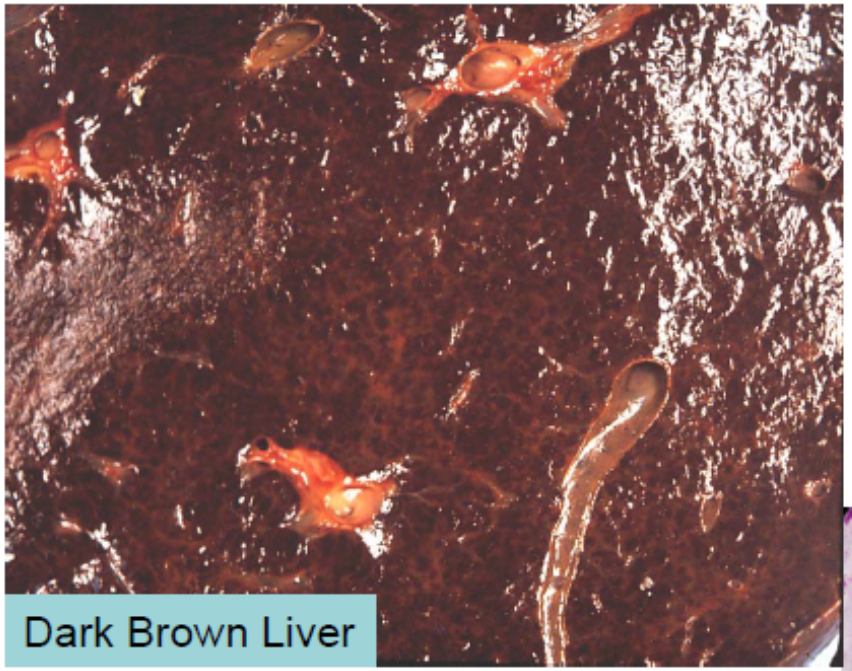
Metabolic Liver Disorders, (Hereditary) Hemochromatosis: A Sensing Defect

Iron Overload: Can't stop absorbing the damn stuff

- Background/Presentation:
  - AR disorder of intestinal iron absorption
    - Cannot regulate iron excretion, only absorption
  - Excess iron deposits and damages multiple organs including liver, heart, pancreas, joints, pituitary/hypothalamus, skin

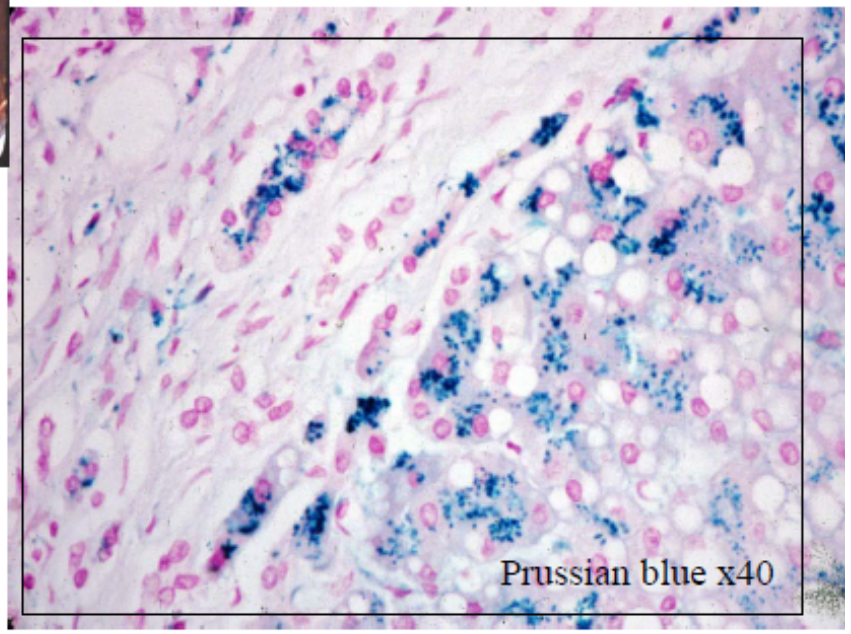
- Diagnosis:
  - Elevated Transferrin Saturation (Fe/TIBC; >50%)
  - Elevated Ferritin (storage form)
  - HFE Gene (chrom 6; C282Y and H63D)
  - Liver bx: increased stainable iron (Prussian blue stain)

Hemochromatosis



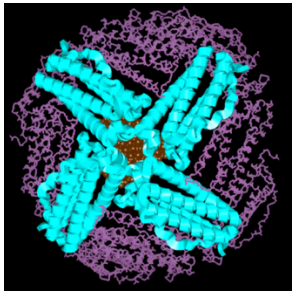
Dark Brown Liver

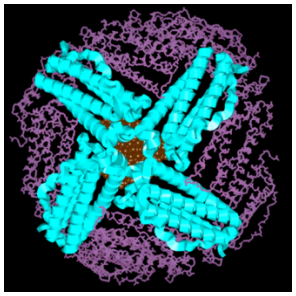
H&Ex10



Detects iron in biopsy specimens

Prussian Blue ⇒ Iron





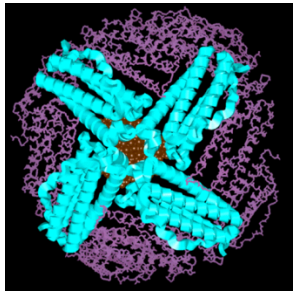
	Serum iron (µg/dL)	TIBC (µg/dL)	Transferrin saturation (%)	Ferritin (µg/dL)
Normal	60-180	230-370	20-50	20-200
Hemochromatosis	>180	<300	>50	>300

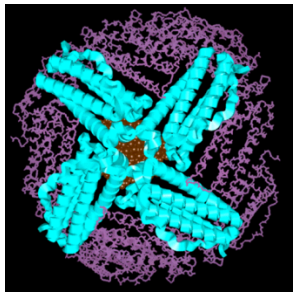
Seats available

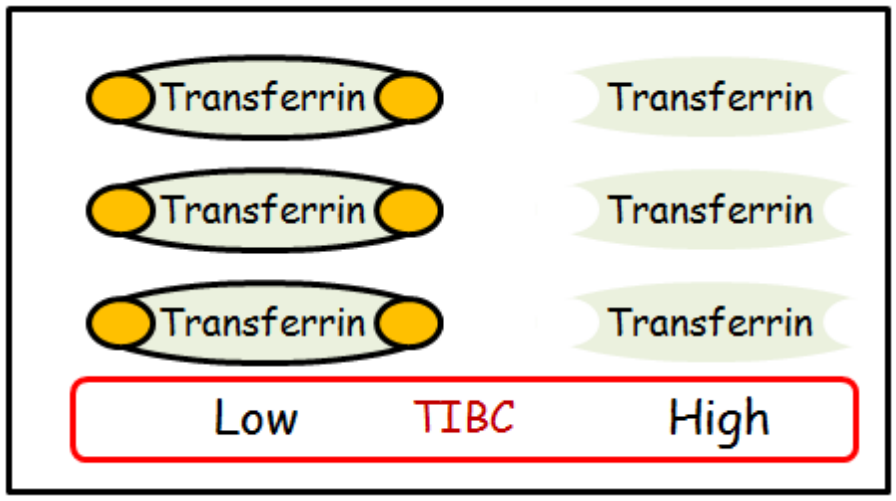
Easy

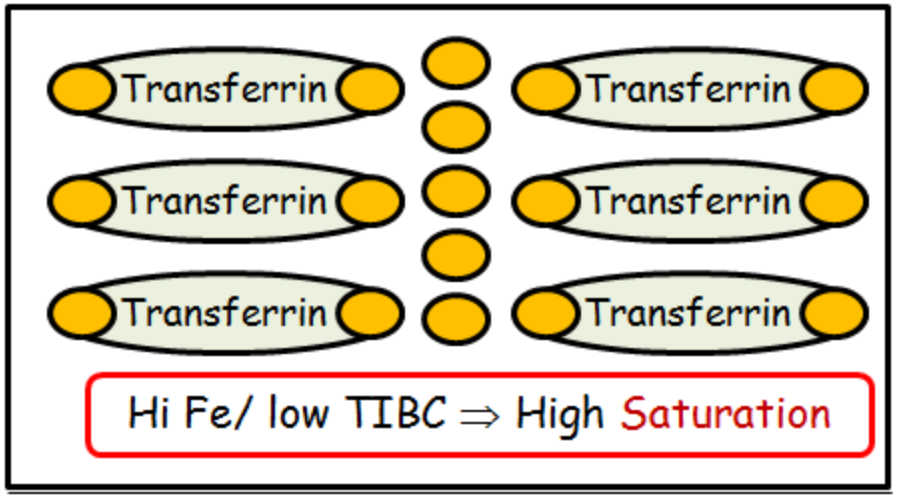
Easy

No Seats available







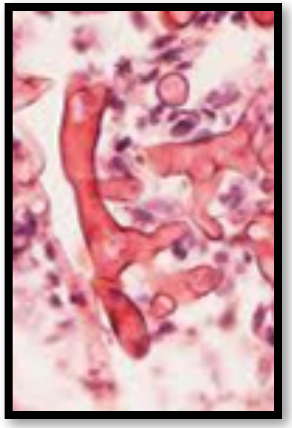


Phlebotomy and Chelation

American Red Cross

Together, we can save a life

Deferoxamine



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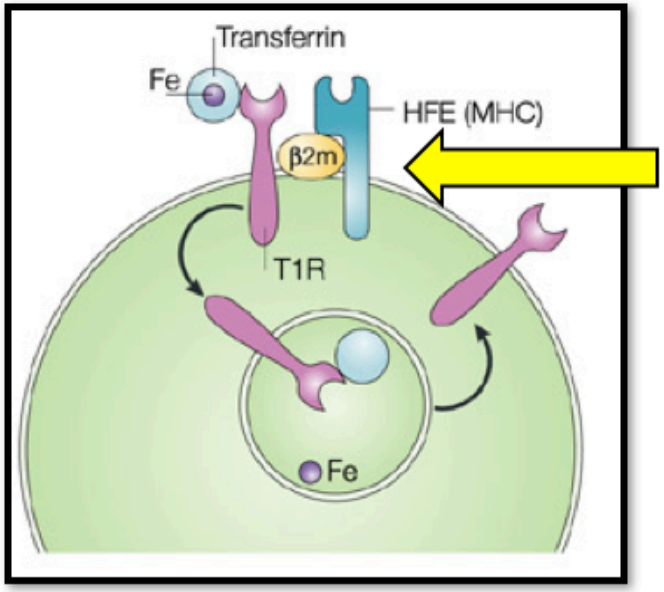

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