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Iron Overload Disorders

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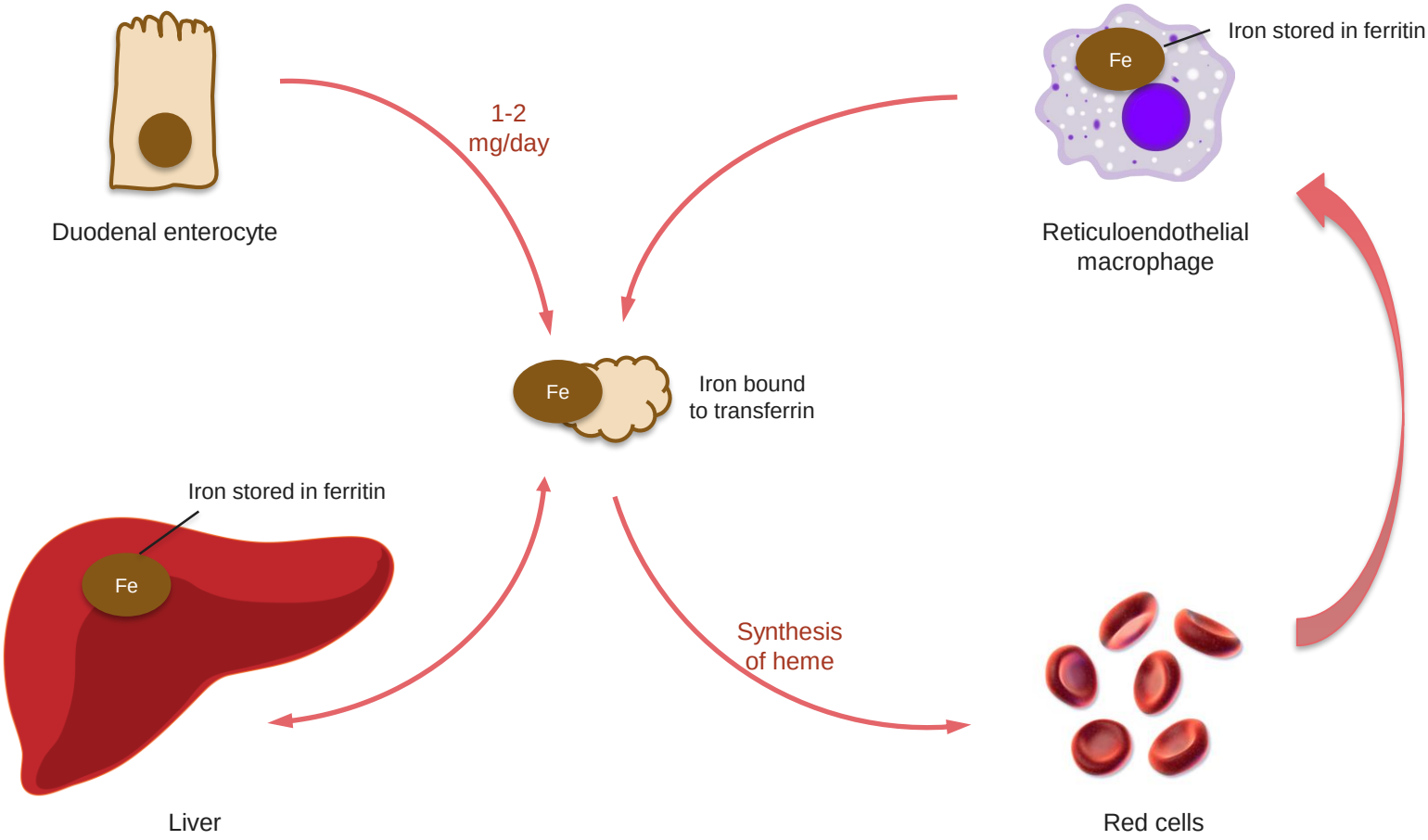
Outline

- Iron metabolism and common iron overload disorders
- Clinical presentation of iron overload disorders
- Diagnostic tests
- Treatment

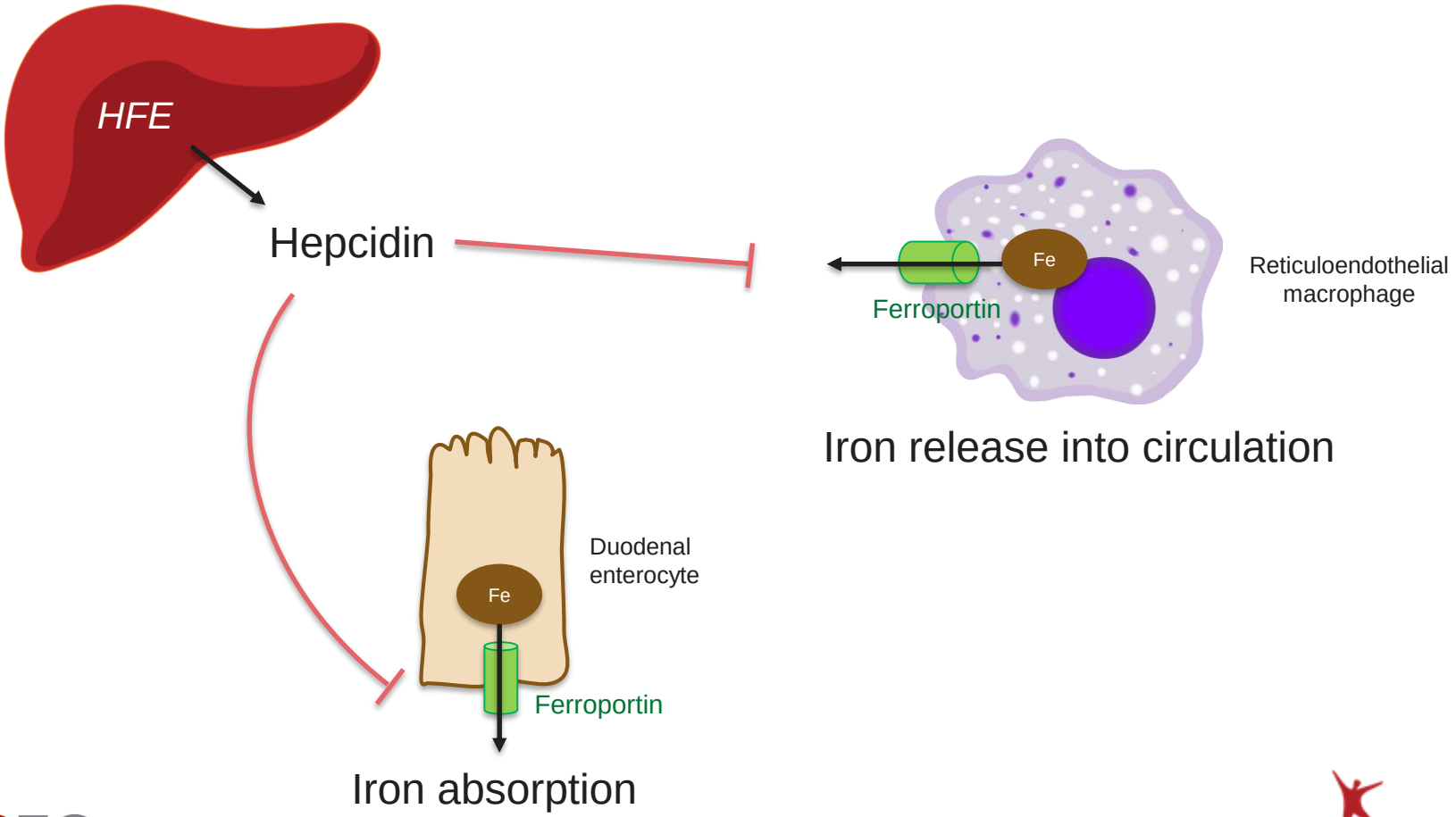
Iron Metabolism



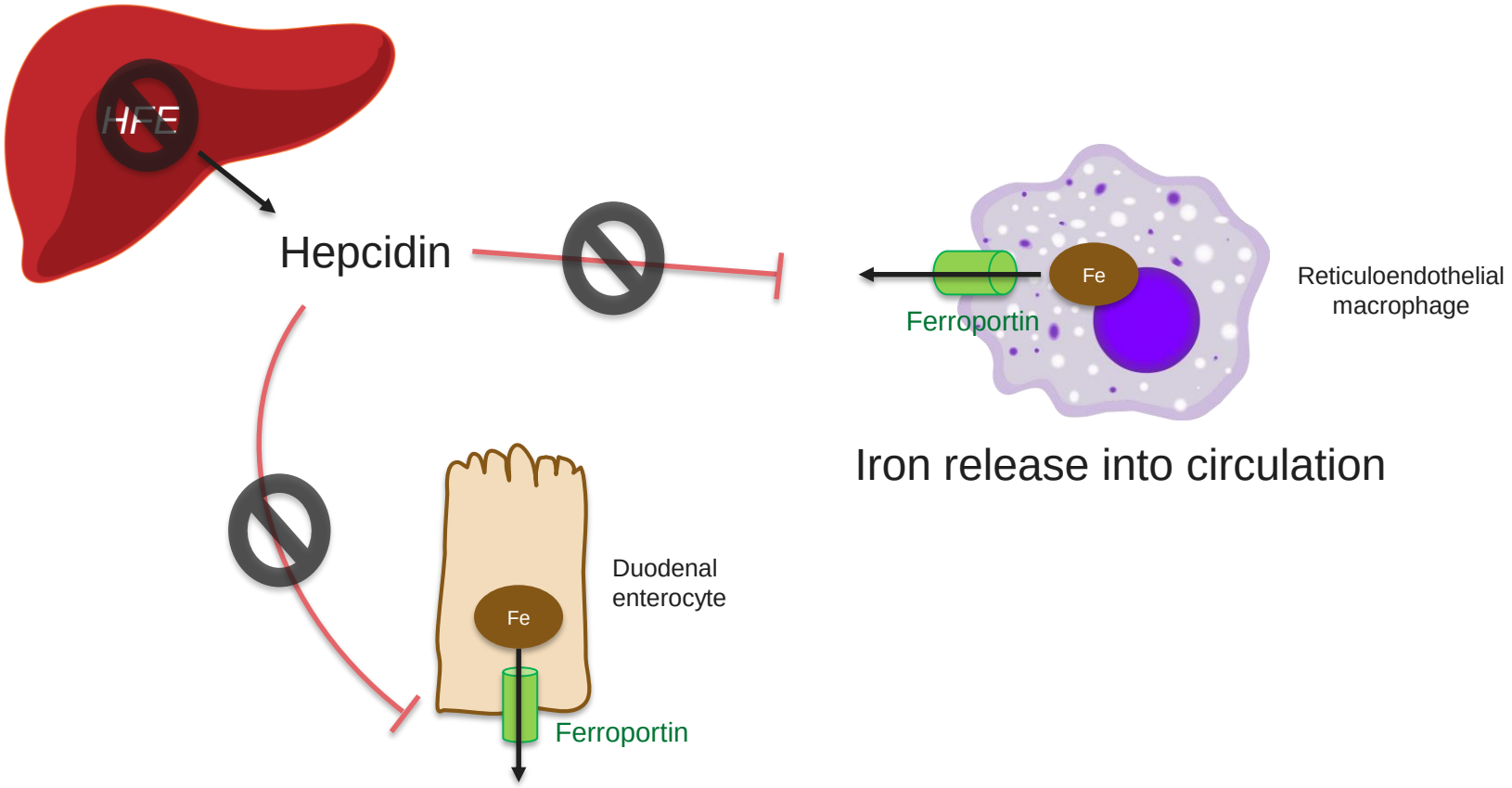
Iron Overload Disorders

- Hereditary hemochromatosis (HH)
- Disorders of erythroid maturation
- Defects of iron transport

Hereditary Hemochromatosis



Hereditary Hemochromatosis



Hereditary Hemochromatosis

- Most common form: HFE-associated hereditary hemochromatosis
  - H: hemochromatosis
  - Fe: Iron
- 80-90% of patients are C282Y homozygotes
- Prevalence of C282Y homozygosity
  - 1 in 200 persons of northern European ancestry
- Only a small portion of C282Y homozygous subjects develop clinical disease.
- Other forms of hemochromatosis:
  - Mutations in transferrin receptor 2 (*TFR2*)
  - Mutations in ferroportin
  - Juvenile hemochromatosis

Disorders of Erythroid Maturation

- Thalassemias, congenital sideroblastic anemias, aplastic anemias

- Secondary iron overload
  - Reduced utilization of iron
  - Down-regulation of hepcidin
  - Frequent transfusion (200-250mg iron per unit of blood)

Defects of Iron Transport

- Hypotransferrinemia
  - Autosomal recessive condition
  - Reduced transferrin concentration
  - Insufficient delivery of transferrin-bound iron for the synthesis of heme

- Aceruloplasminemia
  - Loss of ceruloplasmin ferroxidase activity
  - Decreased loading of iron onto transferrin

Clinical Presentation of Iron Overload

- Liver disease
  - Liver is the primary organ of iron storage
  - 10-25% of patients develop hepatic fibrosis
  - 4-6% of patients develop cirrhosis
- Endocrine disease
  - Accumulation of iron in beta cells (pancreas)
- Cardiac involvement
  - Accumulation of iron in the heart

Diagnostic Tests of Iron Overload

- Screening tests:
  - Transferrin saturation
  - Serum ferritin

- Confirmatory/definitive tests:
  - Liver biopsy
  - *HFE* genetic testing
  - MRI

Screening Tests of Iron Overload

- **Transferrin saturation**
  - Calculated:

$$\frac{\text{Serum Fe } (\frac{\mu g}{dL})}{\text{Transferrin}(\frac{mg}{dL})} \text{x factor}(\sim 71)$$

  - Useful in patients with HH
  - Repeated testing or overnight fasting recommended due to high diurnal variation
  - Cutoff: 45%

- **Serum ferritin**
  - Reflects the body Fe content
  - Useful in all patients with iron overload
  - Monitor the effect of treatment
  - Not specific: Acute phase protein
  - Cutoff: 200µg/L women
    300µg/L men

Treatment of Iron Overload

- Phlebotomy
  - Treatment selected in the absence of anemia
  - Applicable in most forms of HH
  - May trigger excessive iron absorption
- Chelation
  - Treatment selected in iron-loading anemias
  - FDA-approved iron chelators: Deferoxamine, deferiprone, deferasirox
  - Excretion of tissue iron through urine or feces by forming complexes

Points to Remember

- There are three major categories of iron overload disorders: hereditary hemochromatosis, disorders of erythroid maturation, and defects of iron transport.
- Major organs affected by iron overload include liver, pancreas and heart.
- Laboratory testing is important for the early diagnosis of iron overload. Two screening tests include transferrin saturation and serum ferritin.
- Patients are treated with therapeutic phlebotomy in the absence of anemia and with iron chelation if they have iron loading anemias.

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