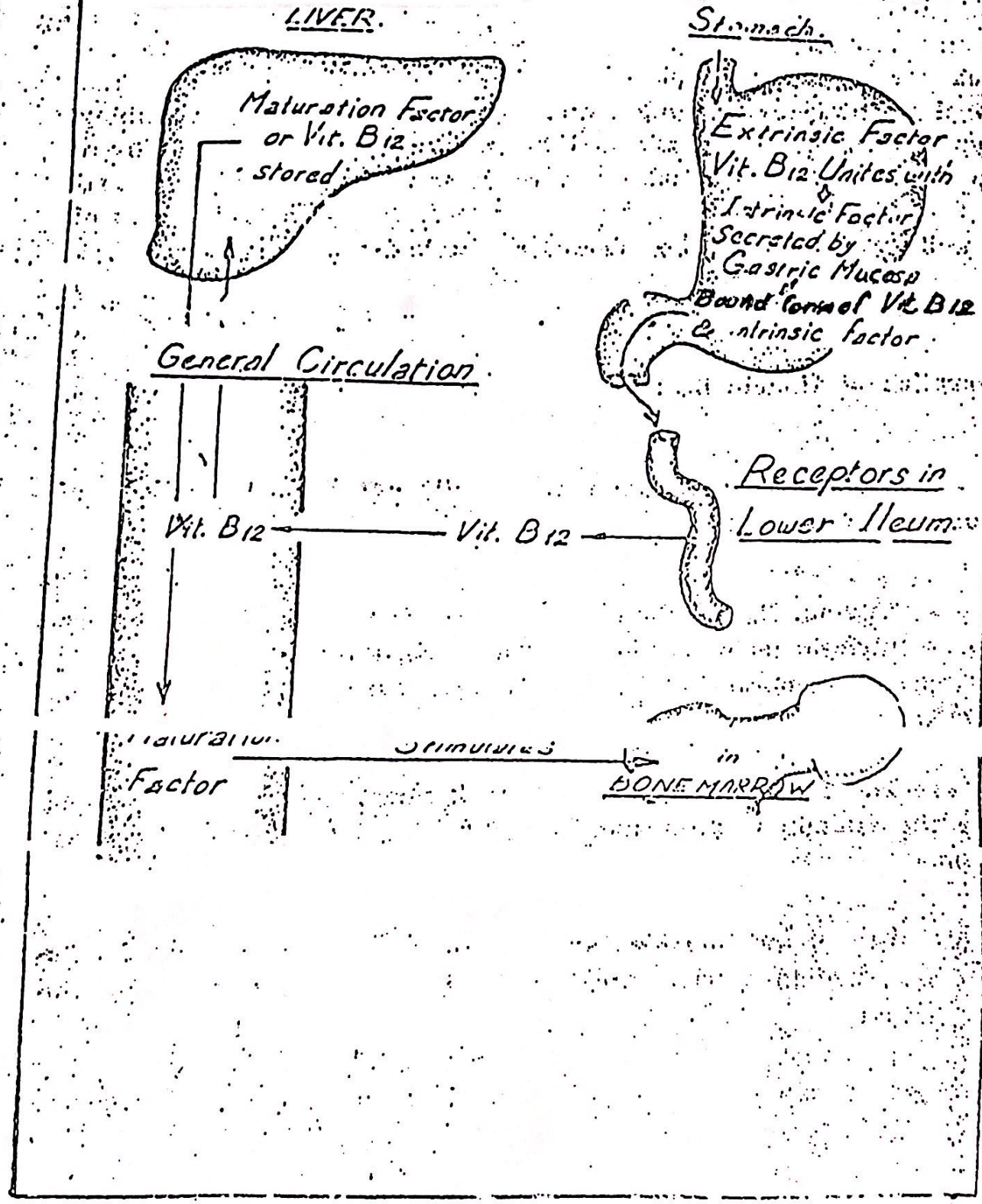


Fig. 11 : Absorption, storage and action of vit. B_{12}

Causes of vitamin B_{12} deficiency

1. VEGANISM
2. MALABSORPTION

a- gastric causes

Congenital lack of IF
Total or partial gastrectomy

b. intestinal causes

Chronic tropical sprue
Ileal resection

Causes of folate deficiency

1- Inadequate dietary intake

2- Malabsorption

Coeliac disease, jejunal resection, tropical sprue

3- Increased requirement

Pregnancy, premature infants, chronic haemolytic anaemias

IRON REQUIREMENTS

The amount of iron required each day to compensate for losses from the body and growth varies with age and sex; it is highest in pregnancy and in adolescent and menstruating females (Table 2.3). These groups, therefore, are particularly likely to develop iron deficiency if there is additional iron loss or prolonged reduced intake.

Table 2.3 Estimated daily iron requirements. Units are mg/day.

	Urine, sweat, faeces	Menses	Pregnancy	Growth	Total
Adult male	0.5–1				0.5–1
Post-menopausal female					
Menstruating female*	0.5–1	0.5–1			1–2
Pregnant female*	0.5–1		1–2		1.5–3.0
Children (average)	0.5			0.6	1
Female (age 12–15)*	0.5–1	0.5–1		0.6	1–2.5

*These groups more likely to develop iron deficiency

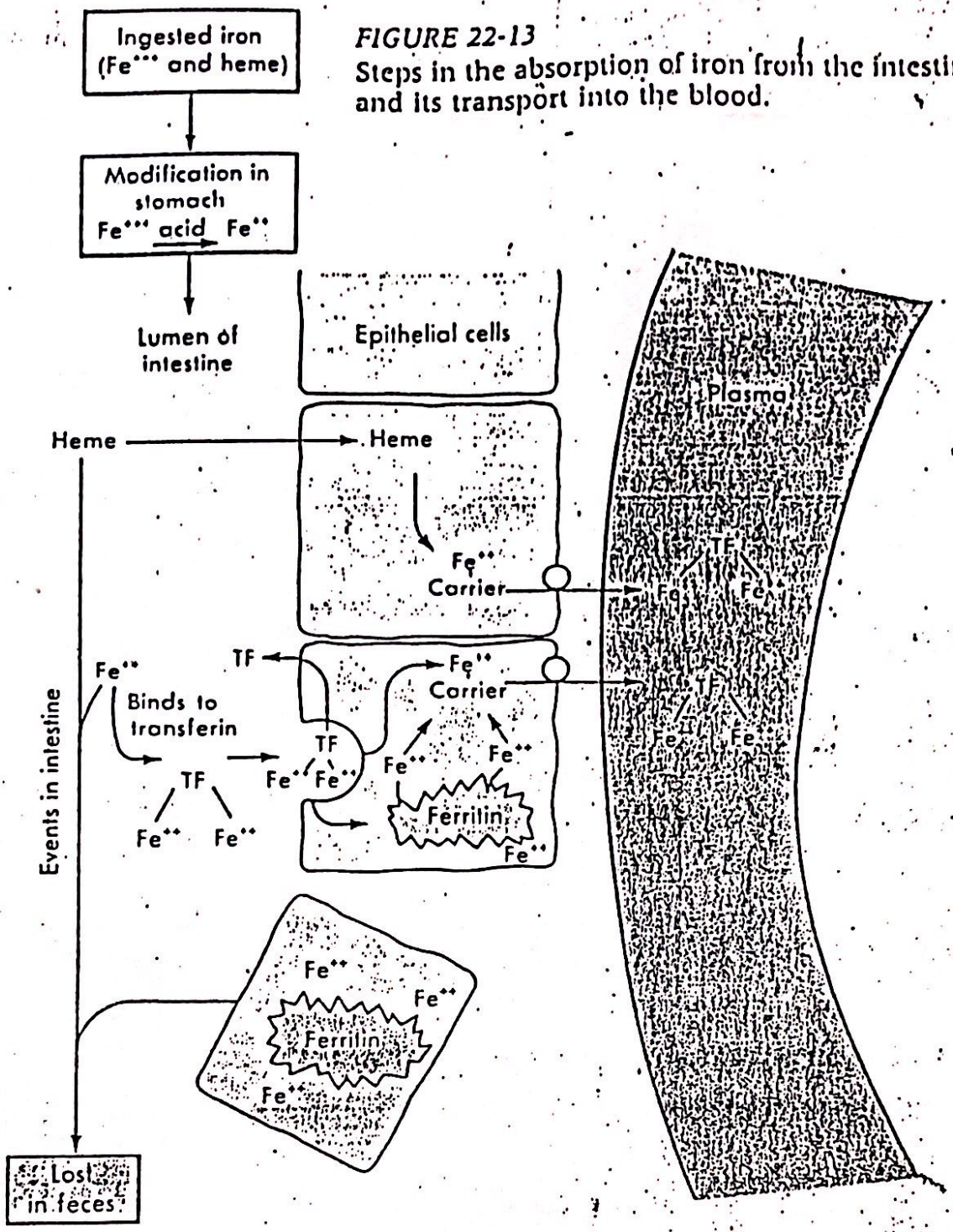


FIGURE 22-13
Steps in the absorption of iron from the intestine and its transport into the blood.

Table 2.2 Iron absorption.

Factors favouring	Factors reducing
1 Ferrous form	1 Ferric form
2 Inorganic iron	2 Organic iron
3 Acids—HCl, vitamin C	3 Alkalis—antacids, pancreatic secretions
4 Solubilising agents—e.g. sugars, amino acids	4 Precipitating agents—phytates, phosphates
5 Iron deficiency	5 Iron excess
6 Increased erythropoiesis	6 Decreased erythropoiesis
7 Pregnancy	7 Infection
8 Primary haemachromatosis	8 Tea
	9 Desferrioxamine

Table 2.1 The distribution of body iron.

	Amount of iron in average adult		
	Male (g)	Female (g)	% of total
Haemoglobin	2.4	1.7	65
Ferritin and haemosiderin	1.0 (0.3–1.5)	0.3 (0–1.0)	30
Myoglobin	0.15	0.12	3.5
Haem enzymes (e.g. cytochromes, catalase, peroxidases, flavoproteins)	0.02	0.015	0.5
Transferrin-bound iron	0.004	0.003	0.1

Table 2.4 Causes of iron deficiency.

1 BLOOD LOSS
Uterine.
Gastrointestinal. e.g. oesophageal varices, hiatus hernia, peptic ulcer, aspirin ingestion, partial gastrectomy, carcinoma of stomach or caecum, colon or rectum, hookworm, angiodysplasia, colitis, piles, diverticulosis, etc.
Rarely haematuria, haemoglobinuria, pulmonary haemosiderosis, self-inflicted blood loss.

2 INCREASED DEMANDS (see also Table 2.3)
Prematurity.
Growth.
Child-bearing.

3 MALABSORPTION
e.g. gastrectomy, coeliac disease.

4 POOR DIET
A contributory factor in many countries but rarely the sole cause.

IRON METABOLISM

Because iron is important for the formation not only of hemoglobin but also of other essential elements in the body (e.g., *myoglobin, cytochromes, cytochrome oxidase, peroxidase,* and *catalase*), it is important to understand the means by which iron is utilized in the body. The total quantity of iron in the body averages 4 to 5 grams.

Heme and nonheme iron are absorbed in the duodenum by distinct cellular mechanisms

Iron plays several critical roles in human physiology, both in the heme groups of the cytochromes and as a key component of the oxygen-carrying heme moieties of hemoglobin and myoglobin. The most important complication of iron depletion is anemia. Iron overload produces **hemochromatosis**, a not uncommon genetic disease (see the box titled Hemochromatosis).

Dietary iron takes two major forms: iron that is part of a heme moiety and iron that is not. These two types of dietary iron are absorbed by distinctly different mechanisms (Fig. 45.18). Overall iron absorption is low: 10% to 20% of

tosis, a not uncommon genetic disease (see the box titled Hemochromatosis).

Dietary iron takes two major forms: iron that is part of a heme moiety and iron that is not. These two types of dietary iron are absorbed by distinctly different mechanisms (Fig. 45-18). Overall iron absorption is low; 10% to 20% of ingested iron is absorbed. Heme iron is absorbed more efficiently than nonheme iron. Body stores of iron depend almost exclusively on iron absorption because no regulated pathway for iron excretion exists. Except in menstruating women, who require ~50% more iron in their diets, very little iron is lost from the body. Dietary iron comes primarily from meat—especially liver and fish—as well as vegetables. The RDA for iron (Table 45-3) in young adults is ~10 mg/day for men and ~15 mg/day for women.

Nonheme Iron Nonheme iron may be either ferric (Fe^{3+}) or ferrous (Fe^{2+}). Ferric iron tends to form salt complexes with anions quite easily and thus is not readily absorbed; it is not soluble at pH values higher than 3. Ferrous iron does not complex easily and is soluble at pH values as high as 8. Ascorbic acid (vitamin C) forms soluble complexes with iron and reduces iron from the ferric to the ferrous state, thereby enhancing iron absorption. Tannins, present in tea, form insoluble complexes with iron and lower its absorption.

Iron movement does not occur passively but requires one or more proteins to facilitate its movement into and out of cells (especially enterocytes, hepatocytes, and macrophages),

absorption.

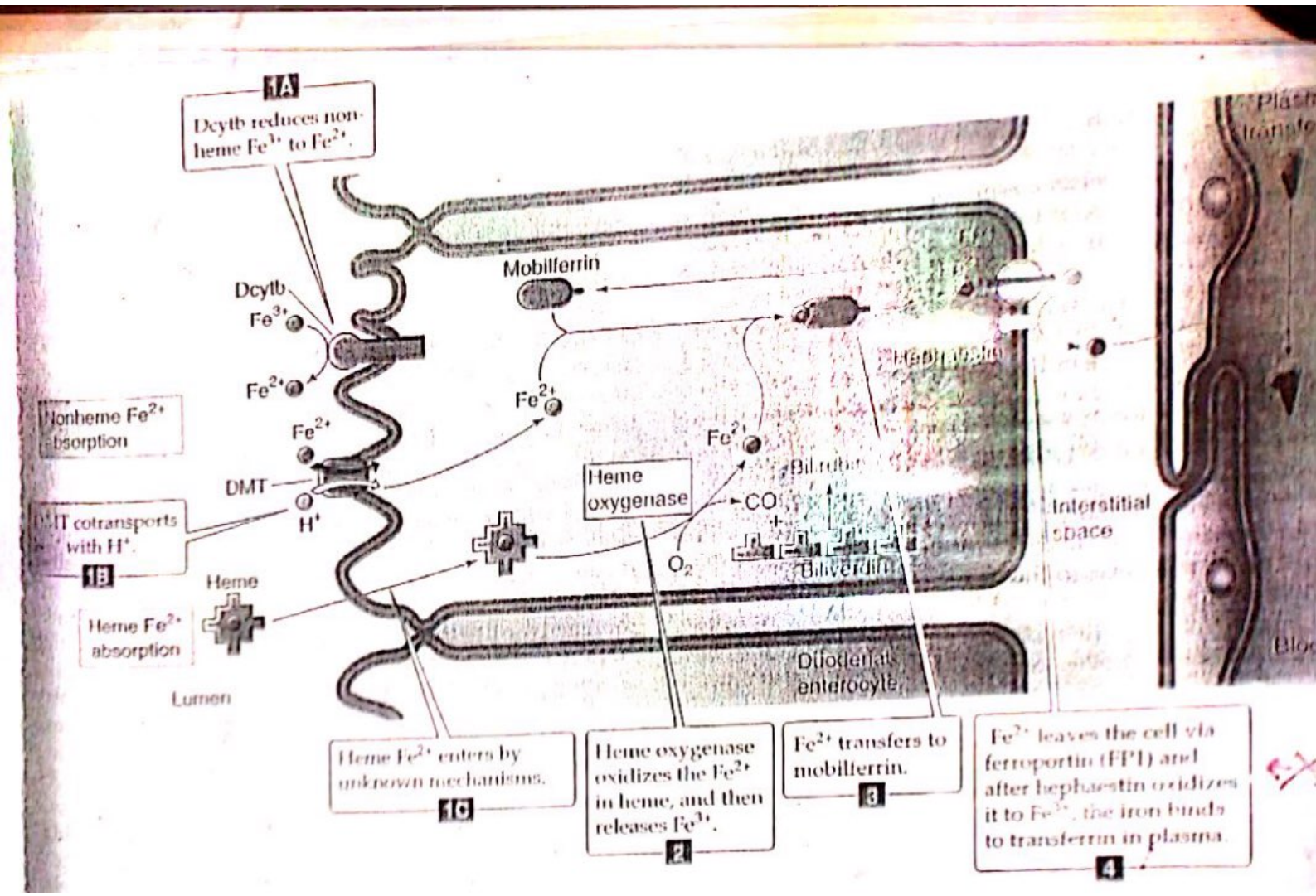
Iron movement does not occur passively but requires one or more proteins to facilitate its movement into and out of cells (especially enterocytes, hepatocytes, and macrophages), as well as for intracellular binding. The absorption of nonheme iron is restricted to the duodenum. The enterocyte takes up nonheme iron across the apical membrane through the **divalent metal transporter** DMT1 (SLC11A2), which cotransports Fe^{2+} and H^+ into the cell (see Chapter 5). DMT1, as well as the oligopeptide cotransporter that we discussed earlier, is unusual in being energized by the inwardly directed H^+ gradient. DMT1 also efficiently absorbs a host of other divalent metals, including several that are highly toxic (e.g., Cd^{2+}, Pb^{2+}). In the case of dietary ferric iron, the **ferric reductase Dcytb**—which is related to cytochrome b—presumably reduces Fe^{3+} to Fe^{2+} at the extracellular surface of the apical membrane before uptake through DMT1.

Fe^{2+} moves into the cytoplasm of the enterocyte, where it binds to **mobilferrin**, an intracellular protein that ferries the Fe^{2+} to the basolateral membrane. The enterocyte then translocates the Fe^{2+} across the basolateral membrane, possibly through **ferroportin transporter** (FP1, also known as IREG1). The mRNA encoding FP1 has an iron-responsive element (see Chapter 4) in its 5′ untranslated region; thus, an increase in intracellular iron levels would be expected to decrease FP1 synthesis. Following the exit of Fe^{2+} from the enterocyte through FP1, the **ferroxidase hephaestin**—a homologue of the plasma protein ceruloplasmin, which carries copper (see Chapter 46)—apparently oxidizes the Fe^{2+} to Fe^{3+}, which then binds to plasma **transferrin** (see Chapter 2) for carriage in the blood.

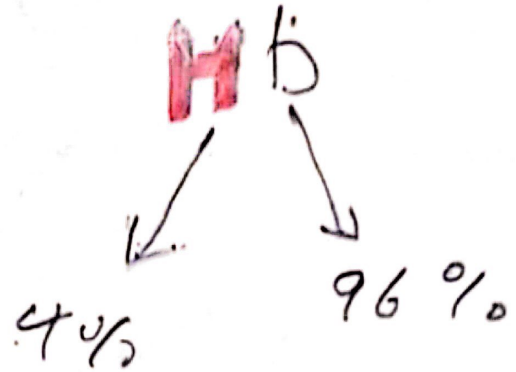
Once in the circulation, nonheme iron bound to transferrin is ultimately deposited in all the tissues of the body, but it has a particular predilection for the liver and reticuloendothelial system. Inside these cells, it binds to the protein apoferritin to form **ferritin**, the major storage form of iron. Smaller amounts of storage iron exist in an insoluble form called *hemosiderin*.

Heme Iron Derived from myoglobin and hemoglobin, heme iron is also absorbed by duodenal epithelial cells. Heme iron enters the cells either by binding to a brush border protein or through an endocytotic mechanism. Inside the cell, **heme oxygenase** enzymatically splits the heme iron, thus releasing free Fe^{3+}, CO, and biliverdin (see Fig. 46-6). The cell reduces the biliverdin to bilirubin, which the liver eventually excretes in bile (see Chapter 46 for the box on jaundice). The enterocyte reduces the Fe^{3+} to Fe^{2+}, which it then handles in the same manner as nonheme iron.

Iron absorption is tightly regulated by the size of existing body iron stores. In physiologically normal subjects, iron [illegible] but is markedly *increased* in states of


1A
Dcytb reduces non-heme Fe^{3+} to Fe^{2+}.
Dcytb
Fe^{3+}
Fe^{2+}
Fe^{2+}
DMT
H^+
Nonheme Fe^{2+} absorption
DMT cotransports Fe^{2+} with H^+.
1B
Heme
Heme Fe^{2+} absorption
Lumen
Mobilferrin
Fe^{2+}
Heme oxygenase
Fe^{2+}
CO
+
O_2
Biliverdin
Duodenal enterocyte
Interstitial space
Heme Fe^{2+} enters by unknown mechanisms.
1C
Heme oxygenase oxidizes the Fe^{2+} in heme, and then releases Fe^{3+}.
2
Fe^{2+} transfers to mobilferrin.
3
Fe^{2+} leaves the cell via ferroportin (FPT) and after hephaestin oxidizes it to Fe^{3+}, the iron binds to transferrin in plasma.
4

(1) Hb



(2) ♂ 16 g/100ml blood
♀ 14 g/ " " "

(3) Each Hb molecule contains 4 subunits 2 α = 141 a.a
2 β = 146 a.a

(4) 65% of Hb synthesis in Erythroblasts,
35% in the reticulocytes.

See next page,

① Hb

4% 96%

② ♂ → 16 g / 100 ml blood.

♀ → 14 g / 100 ml blood.

③ Each Hb molecule contains 4 Subunits
- 2α = 141 amino acids.
- 2β = 146 amino acids.

④ 65% Hb Synthesis in Erythroblast.

35% Hb Synthesis in the Reticulocytes.