QUESTION 3
The predominant site of gastrointestinal absorption of dietary iron is the:
A. proximal small intestine.
B. gastric fundus.
C. terminal ileum.
D. pyloric antrum.
E. colon.

THE IRON CYCLE IN HUMANS

- Iron absorbed from the diet or released from stores circulates in the plasma bound to transferrin, the iron transport protein.

- The iron-transferrin complex circulates in the plasma until the iron-carrying transferrin interacts with specific transferrin receptors on the surface of marrow erythroid cells. Diferric transferrin has the highest affinity for transferrin receptors; apotransferrin (transferrin not carrying iron) has very little affinity. While transferrin receptors are found on cells in many tissues within the body—and all cells at some time during development will display transferrin receptors—the cell having the greatest number of receptors (300,000 to 400,000/cell) is the developing erythroblast.

- Once the iron-bearing transferrin interacts with its receptor, the iron-transferrin-receptor complex is internalized via clathrin-coated pits and transported to an acidic endosome, where the iron is released at the low pH. The iron is then made available for heme synthesis while the transferrin-receptor complex is recycled to the surface of the cell, where the bulk of the transferrin is released back into the circulation and the transferrin receptor reanchors into the cell membrane. At this point a certain amount of the transferrin receptor protein may be released into circulation.

- Within the erythroid cell, iron that is in excess of the amount needed for hemoglobin synthesis binds to a storage protein, apoferritin, forming ferritin. This mechanism of iron exchange also takes place in other cells of the body expressing transferrin receptors, especially liver parenchymal cells where the iron can be incorporated into heme-containing enzymes or stored. The iron incorporated into hemoglobin subsequently enters the circulation as new red cells are released from the bone marrow. The iron is then part of the red cell mass and will not become available for reutilization until the red cell dies.

- In a normal individual, the average red cell life span is 120 days. Thus, 0.8 to 1.0% of red cells turn over each day. At the end of its life span, the red cell is recognized as senescent by the cells of the reticuloendothelial (RE) system, and the cell undergoes phagocytosis. Once within the RE cell, the hemoglobin from the ingested red cell is broken down, the globin and other proteins are returned to the amino acid pool, and the iron is shuttled back to the surface of the RE cell, where it is presented to circulating transferrin.

- Since each milliliter of red cells contains 1 mg of elemental iron, the amount of iron needed to replace those red cells lost through senescence amounts to 16 to 20 mg/d (assuming an adult with a red cell mass of 2 L). Any additional iron required for daily red cell production comes from the diet. Normally, an adult male will need to absorb at least 1 mg of elemental iron daily to meet needs, while females in the childbearing years will need to absorb an average of 1.4 mg/d.

- However, to achieve a maximum proliferative erythroid marrow response to anemia, additional iron must be available. With markedly stimulated erythropoiesis, demands for iron are increased by as much as six- to eightfold. With hemolytic anemias, the rate of red cell destruction is increased, but the iron recovered from the red cells is efficiently reutilized for hemoglobin synthesis. In contrast,
with blood loss anemia the rate of red cell production is limited by the amount of iron that can be mobilized from ferritin and hemosiderin stores. Typically, the rate of mobilization under these circumstances will not support red cell production more than 2.5 to 3 times normal. If the delivery of iron to the stimulated marrow is suboptimal, the marrow’s proliferative response is blunted and normal hemoglobin synthesis is impaired. The result is a hypoproliferative marrow accompanied by microcytic, hypochromic anemia.

- While blood loss or hemolysis places a demand for iron to be supplied to the erythroid marrow, other conditions such as inflammation interfere with iron release from stores and can result in a rapid decrease in the serum iron.

- The balance of iron metabolism in the organism is tightly controlled and designed to conserve iron for reutilization. There is no excretory pathway for iron, and the only mechanisms by which iron is lost from the body are blood loss (via gastrointestinal bleeding, menses, or other forms of bleeding) and the loss of epidermal cells from the skin and gut. Normally, the only route by which iron comes into the body is via absorption from food (dietary iron intake) or from medicinal iron taken orally. Iron may also enter the body through red cell transfusions or injection of iron complexes. The margin between the amount of iron available for absorption and the requirement for iron in growing infants and the adult female is narrow. The narrowness of this margin accounts for the great prevalence of iron deficiency worldwide—currently estimated at one-half billion people.

- External iron exchange—the amount of iron required from the diet to replace losses—averages about 10% of body iron content a year in men and 15% in women of childbearing age, equivalent to 1.0 and 1.4 mg of elemental iron daily, respectively. Dietary iron content is closely related to total caloric intake (approximately 6 mg of elemental iron per 1000 calories). Iron bioavailability is affected by the nature of the foodstuff, with heme iron (e.g., red meat) being most readily absorbed. In the United States, the average iron intake in an adult male is 15 mg/d with 6% absorption; for the average female, the daily intake is 11 mg/d with 12% absorption.

- An individual with iron deficiency can increase iron absorption to about 20% of the iron present in a meat-containing diet but only 5 to 10% of the iron in a vegetarian diet. As a result, nearly one-third of the female population in the United States has virtually no iron stores. Vegetarians are at an additional disadvantage because certain foodstuffs that include phytates and phosphates reduce iron absorption by about 50%.

- When ionizable iron salts are given together with food, the amount of iron absorbed is reduced. This is particularly true with iron in the ferric state. When the percentage of iron absorbed from individual food items is compared with the percentage for an equivalent amount of ferrous salt, iron in vegetables is only about one-twentieth as available, egg iron one-eighth, liver iron one-half, and heme iron one-half to two-thirds. Therefore, liver and heme iron are absorbed nearly as well as iron salt added to food, while the iron in vegetables and eggs is much less available.

- Infants, children, and adolescents may be unable to maintain normal iron balance because of the demands of body growth and lower dietary intake of iron. In pregnancy during the last two trimesters, daily iron requirements increase to 5 to 6 mg. That is the reason why iron supplements are strongly recommended for pregnant women in developed countries.

- **Iron absorption takes place largely in the proximal small intestine and is a carefully regulated process.** For absorption, iron must be taken up by the luminal cell. That process is facilitated by the acidic contents of the stomach, which maintains the iron in solution. At the brush border of the absorptive cell, the ferric iron is converted to the ferrous form by a
Year 2003 Paper one: Questions supplied by Tricia

Ferrireductase. Transport across the membrane is accomplished by divalent metal transporter 1 (DMT 1, also known as Nramp 2 or DCT 1). DMT 1 is a general cation transporter. Once iron is inside the gut cell, the iron may be stored as ferritin or transported through the cell to be released at the basolateral surface to plasma transferrin. It is likely that another transporter acts here in concert with hephaestin, another ferroxidase. Hephaestin is similar to ceruloplasmin, the copper-carrying protein.

• Iron absorption is influenced by a number of physiologic states. Erythroid hyperplasia, for example, stimulates iron absorption, even in the face of normal or increased iron stores. Patients with anemias associated with high levels of ineffective erythropoiesis absorb excess amounts of dietary iron. Over time, this may lead to iron overload and tissue damage. In iron deficiency, iron is much more efficiently absorbed from a given diet; the contrary is true in the presence of iron overload. This is possibly mediated through signals that become fixed before the jejunal crypt cell migrates up the villus to become an absorptive cell. The normal individual can reduce iron absorption in situations of excessive intake or medicinal iron intake; however, while the percentage of iron absorbed goes down, the absolute amount goes up. This accounts for the acute iron toxicity occasionally seen when children ingest large numbers of iron tablets. Under these circumstances, the amount of iron absorbed exceeds the transferrin binding capacity of the plasma, resulting in free iron that affects critical organs such as cardiac muscle cells.